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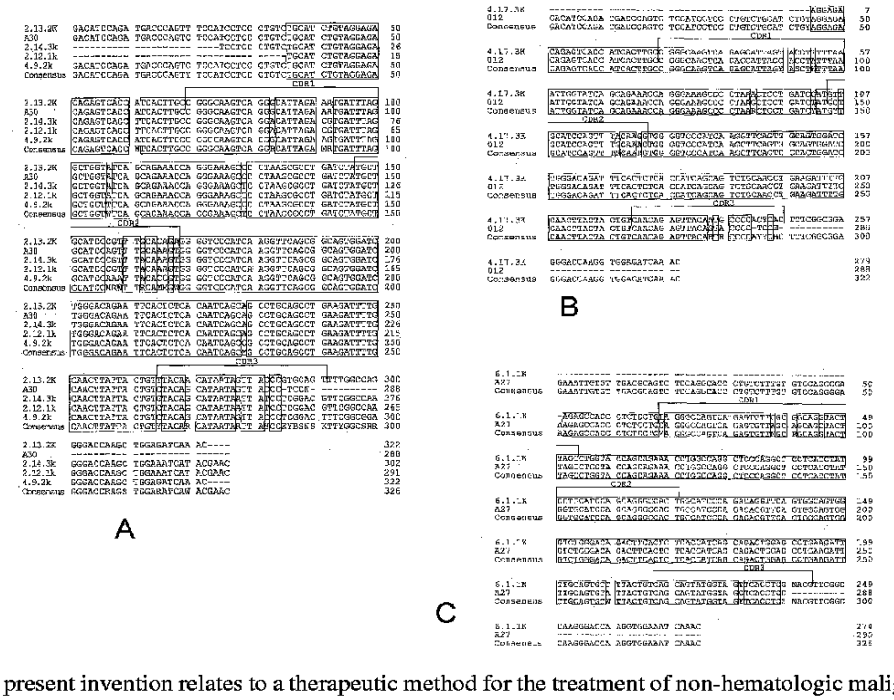
(54) Title: COMBINATION TREATMENT FOR NON-HEMATOLOGIC MALIGNANCIES USING AN ANTI-OGF-1R ANTIBODY



(57) Abstract: The present invention relates to a therapeutic method for the treatment of non-hematologic malignancies comprising administering anti-IGF-1R antibodies, particularly human anti-IGF-1R antibodies, to a patient, in conjunction with the administration of at least one other therapeutic agent. The invention further relates to pharmaceutical compositions comprising these antibodies and methods of using such compositions thereof for treatment.

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COMBINATION TREATMENT FOR NON-HEMATOLOGIC MALIGNANCIES USING AN ANTI-IGF-1R ANTIBODY

Background of the Invention

The present invention relates to a method of treatment for non-hematologic malignancies comprising the administration of anti-insulin-like growth factor I receptor (IGF-1R) antibodies, in conjunction with other therapeutic agents such as chemotherapeutic agents and hormonal therapy.

The insulin-like growth factor (IGF) signaling system plays an important role in the growth and development of many tissues and regulates overall growth. Insulin-like growth factor (IGF-1) is a 7.5-kD polypeptide that circulates in plasma in high concentrations and is detectable in most tissues. IGF-1 stimulates cell differentiation and cell proliferation, and is required by most mammalian cell types for sustained proliferation. These cell types include, among others, human diploid fibroblasts, epithelial cells, smooth muscle cells, T lymphocytes, neural cells, myeloid cells, chondrocytes, osteoblasts and bone marrow stem cells.

The first step in the transduction pathway leading to IGF-1-stimulated cellular proliferation or differentiation is binding of IGF-1 or IGF-2 (or insulin at supraphysiological concentrations) to the IGF-1 receptor. The IGF-1 receptor (IGF-1R) is composed of two types of subunits: an alpha subunit (a 130-135 kD protein that is entirely extracellular and functions in ligand binding) and a beta subunit (a 95-kD transmembrane protein, with transmembrane and cytoplasmic domains). IGF binding proteins (IGFBPs) have growth inhibiting effects by, at least in part, competitively binding IGFs and preventing their association with IGF-1F. The interactions between IGF-1, IGF-2, IGF1R, and IGFBPs affect many physiological and pathological processes such as development, growth and metabolic regulation.

The IGF-1R is initially synthesized as a single chain proreceptor polypeptide that is processed by glycosylation, proteolytic cleavage, and covalent bonding to assemble into a mature 460-kD heterotetramer comprising two alpha-subunits and two beta-subunits. The beta subunit(s) possesses ligand-activated tyrosine kinase activity. This activity is implicated in the signaling pathways mediating ligand action which involve autophosphorylation of the beta-subunit and phosphorylation of IGF-1R substrates.

There is considerable evidence for a role for IGF-1 and/or IGF-1R in the maintenance of tumor cells *in vitro* and *in vivo*. IGF-1R levels are elevated in tumors of lung (Kaiser et al., *J. Cancer Res. Clin. Oncol.* 119: 665-668, 1993; Moody et al., *Life Sciences* 52: 1161-1173, 1993; Macauley et al., *Cancer Res.*, 50: 2511-2517, 1990), breast (Pollack et al., *Cancer Lett.* 38: 223-230, 1987; Foekens et al., *Cancer Res.* 49: 7002-7009, 1989; Cullen et al., *Cancer Res.* 49: 7002-7009, 1990; Arteaga et al., *J. Clin. Invest.* 84: 1418-1423, 1989), prostate and colon (Remaole-Bennet et al., *J. Clin. Endocrinol. Metab.* 75: 609-616, 1992; Guo et al., *Gastroenterol.* 102: 1101-1108, 1992). In addition, IGF-1 appears to be an autocrine stimulator of human gliomas (Sandberg-Nordqvist et al., *Cancer Res.* 53: 2475-2478, 1993),

while IGF-1 stimulated the growth of fibrosarcomas that overexpressed IGF-1R (Butler et al., *Cancer Res.* 58: 3021-27, 1998). In addition, individuals with "high normal" levels of IGF-1 have an increased risk of common cancers compared to individuals with IGF-1 levels in the "low normal" range (Rosen et al., *Trends Endocrinol. Metab.* 10: 136-41, 1999). For a review of the role IGF-1/IGF-1 receptor interaction plays in the growth of a variety of human tumors, see Macaulay, *Br. J. Cancer*, 65: 311-320, 1992.

Numerous classes of antineoplastic agents are currently in use. Docetaxel, one of a group of drugs called "taxanes," which are derived from the bark and needles of yew trees, is the first anticancer agent to show a significantly higher response rate than doxorubicin, a very active agent and widely used chemotherapy in the first-line treatment of metastatic breast cancer. Docetaxel also is the first chemotherapy drug as a single agent to demonstrate increased survival among patients with advanced breast cancer compared to the combination of mitomycin C and vinblastine, a commonly used regimen in this patient population. Median time to progression and time to treatment failure were significantly longer for docetaxel than for mitomycin C in combination with vinblastine, and the one-year survival rate significantly greater. Promising results have also been recorded for docetaxel in other human malignancies, such as ovarian, lung, head and neck, gastric and pancreatic cancers.

Paclitaxel, also a taxane, binds to microtubules and prevents their molecular disassembly, thereby inhibiting mitosis (cell division). With the spindle still in place the cell cannot divide into daughter cells. Paclitaxel is most effective against ovarian carcinomas and advanced breast carcinomas.

Hormonal therapy can be very effective in lowering the risk of recurrence for women with hormone-receptor-positive breast cancer. Tamoxifen is the hormonal therapy that has been around the longest—nearly 30 years. It blocks the effect of estrogen on breast cancer cells, keeping the cells from growing. Tamoxifen can reduce recurrence by 40-50% in post-menopausal women, and by 30-50% in pre-menopausal women. It also lowers the risk of a new breast cancer developing in the unaffected breast, and can slow down the progression of advanced disease.

In recent years, aromatase inhibitors have been used as hormonal therapy. This type of therapy is recommended only for postmenopausal women with hormone-receptor-positive breast cancer. It works by blocking the production of estrogen in muscle and fat tissue, which is the main source of estrogen in women beyond menopause, after which the ovaries stop making significant levels of estrogen.

Prostate cancer is the most common cancer and the second cause of cancer death in men in the United States. About 10% of the initial cases of prostate cancer present with metastatic disease. However, in the rest, metastases will develop despite treatment with surgery, radiation or medical therapy, and those metastases will eventually become refractory

to hormonal treatment. The use of chemotherapy in hormone refractory (androgen independent) progressive prostate cancer (HRPC) has been characterized historically by poor efficacy and high toxicity. Newer regimens containing docetaxel have shown a survival benefit over previous palliative regimens. Despite this positive trend, the median survival of HRPC patients treated with docetaxel and prednisone is only 18.9 months; clearly, more effective regimens are required for the treatment of HRPC patients.

Although some currently available anti-cancer treatments have been successful, complete responses to these treatments are infrequently observed, and the patient population refractory to these treatments is still large. Thus, development of new therapeutic regimens, particularly those capable of augmenting or potentiating the anti-tumor activity of other anti-neoplastic agents, is necessary.

In view of the roles that IGF-1 and IGF-1R have in such disorders as cancer and other proliferative disorders when IGF-1 and/or IGF-1R are overexpressed, antibodies to IGF-1R have been produced that block binding of IGF-1 or IGF-2 to IGF-1R. Such antibodies are described, for example, in International Patent Application No. WO 02/053596, published July 11, 2002; International Patent Application Nos. WO 05/016967 and WO 05/016970, both published February 24, 2005; International Patent Application No. WO 03/106621, published December 24, 2003; International Patent Application No. WO 04/083248, published September 30, 2004; International Patent Application No. WO 03/100008, published December 4, 2003; International Patent Publication WO 04/087756, published October 14, 2004; and International Patent Application No WO 05/005635, published January 26, 2005. Because of their ability to block a tumor cell survival pathway, it is desirable to use such anti-IGF-1R antibodies to treat cancer, particularly non-hematological malignancies, in patients to obtain an improved clinical benefit relative to standard cancer treatment regimes alone.

Summary of the Invention

The present invention is directed to a method for the treatment of an advanced non-hematologic malignancy in a patient in need of such treatment comprising the step of administering to the patient a therapeutically effective amount of an anti-IGF-1R antibody.

More particularly, the present invention is directed to a method comprising the step of administering to the patient an antibody that specifically binds to IGF-1R in combination with a therapeutically effective amount of at least one agent selected from the group consisting of an alkylating agent, a folate antagonist, a pyrimidine antagonist, a cytotoxic antibiotic, a platinum compound, a taxane, a vinca alkaloid, a topoisomerase inhibitor, an EGFR inhibitor, and a hormonal therapy agent. Preferably the antibody is one that specifically binds to human IGF-1R.

In a preferred embodiment of the present invention, the anti-IGF-1R antibody has the following properties: (a) a binding affinity for human IGF-1R of K_d of 8 x 10^{-9} or less, and (b) inhibition of binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100 nM.

In another preferred embodiment of the present invention, the anti-IGF-1R antibody comprises (a) a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3 of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1, and (b) a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3 of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1, or (c) sequences having changes from the CDR sequences of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1, said sequences being selected from the group consisting of conservative changes, wherein the conservative changes are selected from the group consisting of replacement of nonpolar residues by other nonpolar residues, replacement of polar charged residues by other polar uncharged residues, replacement of polar charged residues by other polar charged residues, and substitution of structurally similar residues; and non-conservative substitutions, wherein the non-conservative substitutions are selected from the group consisting of substitution of polar charged residue for polar uncharged residues and substitution of nonpolar residues for polar residues, additions and deletions.

The present invention is also directed to a pharmaceutical composition for the treatment of a non-hematologic malignancy comprising (a) a therapeutically effective amount of an antibody that specifically binds IGF-1R, (b) a therapeutically effective amount of at least one agent selected from the group consisting of an alkylating agent, a folate antagonist, a pyrimidine antagonist, a cytotoxic antibiotic, a platinum compound, a taxane, a vinca alkaloid, a topoisomerase inhibitor, an EGFR inhibitor, and a hormonal therapy agent; and (c) a pharmaceutically acceptable carrier.

Detailed Description Of The Drawings

Figs. 1A-1C show alignments of the nucleotide sequences of the light chain variable regions from six human anti-IGF-1R antibodies to each other and to germline sequences. Fig. 1A shows the alignment of the nucleotide sequences of the variable region of the light chain (VL) of antibodies 2.12.1 (SEQ ID NO: 1) 2.13.2 (SEQ ID NO: 5), 2.14.3 (SEQ ID NO: 9) and 4.9.2 (SEQ ID NO: 13) to each other and to the germline Vκ A30 sequence (SEQ ID NO: 39). Fig. 1B shows the alignment of the nucleotide sequence of VL of antibody 4.17.3 (SEQ ID NO: 17) to the germline Vκ O12 sequence (SEQ ID NO: 41). Fig. 1C shows the alignment of the nucleotide sequence of VL of antibody 6.1.1 (SEQ ID NO: 21) to the germline Vκ A27 sequence (SEQ ID NO: 37). The alignments also show the CDR regions of the VL from each antibody. The consensus sequences for Figs. 1A-1C are shown in SEQ ID NOS: 53-55, respectively.

Figs. 2A-2D show alignments of the nucleotide sequences of the heavy chain variable regions from six human anti-IGF-1R antibodies to each other and to germline sequences. Fig. 2A shows the alignment of the nucleotide sequence of the VH of antibody 2.12.1 (SEQ ID NO: 3) to the germline VH DP-35 sequence (SEQ ID NO: 29). Fig. 2B shows the alignment of the nucleotide sequence of the VH of antibody 2.14.3 (SEQ ID NO: 11) to the germline VIV-4/4.35 sequence (SEQ ID NO: 43). Figs. 2C-1 and 2C-2 show the alignments of the nucleotide sequences of the VH of antibodies 2.13.2 (SEQ ID NO: 7), 4.9.2 (SEQ ID NO: 15) and 6.1.1 (SEQ ID NO: 23) to each other and to the germline VH DP-47 sequence (SEQ ID NO: 31). Fig. 2D shows the alignment of the nucleotide sequence of the VH of antibody 4.17.3 (SEQ ID NO: 19) to the germline VH DP-71 sequence (SEQ ID NO: 35). The alignment also shows the CDR regions of the antibodies. The consensus sequences for Figs. 2A-2D are shown in SEQ ID NOS: 56-59, respectively.

Fig. 3A shows the number of mutations in different regions of the heavy and light chains of 2.13.2 and 2.12.1 compared to the germline sequences. Figs. 3A-D show alignments of the amino acid sequences from the heavy and light chains of antibodies 2.13.2 and 2.12.1 with the germline sequences from which they are derived. Fig. 3B shows an alignment of the amino acid sequence of the heavy chain of antibody 2.13.2 (SEQ ID NO: 45) with that of germline sequence DP-47(3-23)/D6-19/JH6 (SEQ ID NO: 46). Fig. 3C shows an alignment of the amino acid sequence of the light chain of antibody 2.13.2 (SEQ ID NO: 47) with that of germline sequence A30/Jk2 (SEQ ID NO: 48). Fig. 3D shows an alignment of the amino acid sequence of the heavy chain of antibody 2.12.1 (SEQ ID NO: 49) with that of germline sequence DP-35(3-11)/D3-3/JH6 (SEQ ID NO: 50). Fig. 3E shows an alignment of the amino acid sequence of the light chain of antibody 2.12.1 (SEQ ID NO: 51) with that of germline sequence A30/Jk1 (SEQ ID NO: 52). For Figures 3B-E, the signal sequences are in italic, the CDRs are underlined, the constant domains are bold, the framework (FR) mutations are highlighted with a plus sign ("+") above the amino acid residue and CDR mutations are highlighted with an asterisk above the amino acid residue.

Figure 4 shows that anti-IGF-1R antibodies 2.13.2 and 4.9.2 reduce IGF-1R phosphotyrosine signal in 3T3-IGF-1R tumors.

Figure 5 shows that anti-IGF-1R antibody 2.13.2 inhibits 3T3-IGF-1R tumor growth *in vivo*.

Detailed Description of the Invention

The present invention are directed to the treatment of non-hematologic malignancies, including breast, lung, brain, skin, ovarian, prostate, head and neck, colorectal, gastric, bladder, renal, esophageal, and pancreatic cancers, as well as solid tumors of childhood. Treatment of both early stage and advanced (metastatic) cancers are within the scope of the

present invention. In preferred embodiments, the method of the present invention is used in the treatment of breast cancer, prostate cancer, and non-small cell lung cancer (NSCLC).

There are many classes of chemotherapeutic drugs currently in use for the treatment of non-hematological malignancies that are suitable for use in the combination therapy of the present invention. For example, alkylating agents are a class of drugs that alkylate DNA, restricting uncoiling and replication of strands. Alkylating agents include cyclophosphamide (CYTOXAN), ifosfamide (IFEX), mechlorethamine hydrochloride (MUSTARGEN), thiotepa (THIOPLEX), streptozotocin (ZANOSAR), carmustine (BICNU, GLIADEL WAFER), lomustine (CEENU), and dacarbazine (DTIC-DOME). A preferred alkylating agent for use in the methods of the present invention is cyclophosphamide.

Folate antagonists bind to dihydrofolate reductase (DHFR) and interfere with pyrimidine (thymidine) synthesis. Methotrexate (MATREX, FOLEX, TREXALL), trimetrexate (NEUTREXIN) and pemetrexed (ARIMTA) are folate antagonists suitable for use in the methods of the present invention. In addition to DHFR, pemetrexed also inhibits thymidylate synthase and glycinamide ribonucleotide formyl transferase, two other folate-dependent enzymes involved in thymidine synthesis.

Pyrimidine antagonists inhibit enzymes involved in pyrimidine synthesis. As pyrimidine analogs, they also interfere with DNA production by competing with normal nucleotides for incorporation into the DNA molecule. Pyrimidine antagonists suitable for use in the methods of the present invention include 5-fluorouracil (5-FU); capecitabine (XELODA), a prodrug of 5'-deoxy-5-fluorouridine (5'-FDUR), which is enzymatically converted to 5-FU *in vivo*; raltitrexed (TOMUDEX); tegafur-uracil (UFTORAL); and gemcitabine (GEMZAR).

Anthracycline antibiotics exert a cytotoxic effect by inhibiting the uncoiling of DNA by intercalation between DNA strands. Anthracyclines and anthracyclines derivatives include doxorubicin hydrochloride (ADRIAMYCIN, RUBEX, DOXIL), epirubicin hydrochloride (ELLENCE, PHARMORUBICIN), daunorubicin (CERUBIDINE, DAUNOXOME), nemorubicin, idarubicin hydrochloride (IDAMYCIN PFS, ZAVEDOS) and mitoxantrone (DHAD, NOVANTRONE). Preferred anthracyclines for use with the present invention include doxorubicin and epirubicin.

Other cytotoxic antibiotics are useful as cancer chemotherapeutic agents and suitable for use in the present invention. These include dactinomycin (actinomycin D, COSMEGEN), plicamycin (MITHRACIN), mitomycin (MUTAMYCIN), and bleomycin (BLENOXANE). Dactinomycin is particularly preferred.

Platinum compounds exert their anti-neoplastic effect by intercalation and intracalation between DNA strands, which inhibits uncoiling of the DNA. Platinum compounds useful in the methods of the present invention include cisplatin (PLATINOL) and carboplatin (PARAPLATIN).

Taxanes promote assembly of microtubules while inhibiting their disassembly into tubulin, thereby blocking a cell's ability to break down the mitotic spindle during mitosis. They have demonstrated significant activity against many solid tumors as single agent therapy and in combination with other chemotherapy agents. One embodiment of the combination therapy of the present invention includes the use of one or more taxanes in combination with the IGF-1R antibody. Suitable taxanes for use in combination with the IGF-1R antibody include docetaxel (TAXOTERE) and paclitaxel (TAXOL).

Vinca alkaloids, like taxanes, are "spindle poisons," acting on the microtubules that form the mitotic spindle. They inhibit mitosis by interfering with microtubule assembly, keeping the spindle from being formed. Vinca alkaloids include vindesine (ELDISINE), vinblastine sulfate (VELBAN), vincristine sulfate (ONCOVIN) and vinorelbine tartrate (NAVELBINE). A preferred vinca alkaloid for use in the methods of the present invention is vinorelbine.

The camptothecin analogs act through inhibition of topoisomerase I, an enzyme critical for DNA replication and packaging. Levels of topoisomerase I are higher in tumor cells than in normal tissue. Camptothecin analogs useful in the methods of the present invention include irinotecan (CAMPTOSAR) and topotecan (HYCAMTIN). Irinotecan is particularly preferred.

Inhibitors of topoisomerase II interfere with the normal DNA breakage resealing process (as do inhibitors of topoisomerase I), and they also interfere with the separation of newly replicated chromosomes, resulting in clastogenic mutation and potential cell death. The anthracyline antibiotics discussed above exhibit topoisomerase II inhibitory activity. Derivatives of podophyllotoxin, an extract of the mayapple that is an antimitotic glucoside) are also topoisomerase II inhibitors. Podophyllotoxin derivatives suitable for use in the present invention include etoposide (VEPESID), etoposide phosphate (ETOPOPHOS), and teniposide (VUMON). Etoposide is particularly preferred.

Compounds directed at inhibition of epidermal growth factor receptor (EGFR) tyrosine kinase (TK) represent a relatively new class of antineoplastic drugs that are useful in the method of the present invention. Many human cancers express members of the EGFR family on the cell surface. When a ligand binds to EGFR, it sets off a cascade of cellular reactions that result in increased cell division and influence other aspects of cancer development and progression, including angiogenesis, metastatic spread, and inhibition of apoptosis. EGFR-TK inhibitors may selectively target one of the members of the EGFR family (EGFR (also known as HER1 or ErbB-1), HER2/neu (also known as ErbB-2), HER3 (also known as ErbB-3), or HER4 (also known as ErbB-4)), or may target two or more of them. EGFR-TK inhibitors suitable for use in the present invention include gefitinib (IRESSA), erlotinib (TARCEVA), trastuzumab (HERCEPTIN), panitumumab (ABX-EGF; Abgenix/Amgen), lapatinib

(GlaxoSmithKline), CI-1033 (Pfizer), GW2016 (GlaxoSmithKline), EKB-569 (Wyeth), PKI-166 (Novartis), CP-724,714 (Pfizer), and BIBX-1382 (Boeringer-Ingelheim). Additional EGFR-TK inhibitors are described in United States Patent Publication No. US 2002-0169165A1, published November 14, 2002.

Another embodiment of the combination therapy of the present invention includes the use of hormonal therapy in combination with the IGF-1R antibody, particularly anti-estrogens in the treatment of breast cancer. Some hormonal treatments compete with estrogen for binding sites in breast tissue. These include tamoxifen citrate (NOLVADEX) and fulvestrant (FASLODEX). Similarly, anti-androgens block testosterone receptors and therefore are useful in the treatment of androgen-dependent prostate cancer.

Other hormone treatments include aromatase inhibitors. This class of hormonal agents inactivate aromatase, the enzyme which converts androgens to estrogens. Examples of aromatase inhibitors suitable for use in combination with the IGF-1R antibody include anastrozole (ARIMIDEX), letrozole (FEMARA), exemestane (AROMASIN), and fadrozole hydrochloride. Exemestane is a particularly preferred aromatase inhibitor for use in the methods of the present invention.

Co-administration of the antibody with an additional therapeutic agent (combination therapy) encompasses administering a pharmaceutical composition comprising both the anti-IGF-1R antibody and one or more additional therapeutic agents, and administering two or more separate pharmaceutical compositions, one comprising the anti-IGF-1R antibody and the other(s) comprising the additional therapeutic agent(s). Further, although co-administration or combination (conjoint) therapy generally mean that the antibody and additional therapeutic agents are administered at the same time as one another, it also encompasses simultaneous, sequential or separate dosing of the individual components of the treatment.

The present invention also encompasses the administration of other therapeutic agents in addition to the first and second components, either concurrently with one or more of those components, or sequentially. Such therapeutic agents include analgesics, cancer vaccines, anti-vascular agents, anti-proliferative agents, and anti-emetic agents. Preferred anti-emetic agents include aprepitant, ondansetron hydrochloride, granisetron hydrochloride, and metoclopramide.

Each administration may vary in its duration from a rapid administration to a continuous perfusion. As a result, for the purposes of the present invention, the combinations are not exclusively limited to those that are obtained by physical association of the constituents, but also to those that permit a separate administration, which can be simultaneous or spaced out over a period of time. The compositions according to the invention are preferably compositions which can be administered parentally. However, these

compositions may be administered orally or intraperitoneally in the case of localized regional therapies.

As will be appreciated by one of skill in the art, the choice of therapeutic agents to be used in combination with IGF-1R antibodies, and the timing of their use, will be determined in part by the type and stage of the cancer that is being treated. For example, in early breast cancer (where the cancer has not spread outside the breast), surgery and radiation are generally followed by adjuvant chemotherapy or adjuvant hormonal therapy, either of which may be combined with IGF-1R antibodies in the methods of the present invention. Typical adjuvant chemotherapy for early breast cancer includes cyclophosphamide, methotrexate and 5-FU ("CMF"); 5-FU, doxorubicin, and cyclophosphamide ("FAC"); docetaxel, doxorubicin, and cyclophosphamide ("TAC"); doxorubicin and cyclophosphamide ("AC"); doxorubicin and cyclophosphamide followed by paclitaxel ("AC and T"); and 5-FU, epirubicin, and cyclophosphamide ("FEC"). Tamoxifen is a preferred hormonal treatment at this stage.

In locally advanced breast cancer, wherein the cancer has spread only to nearby tissues or lymph nodes, the patient is often given chemotherapy prior to surgery and radiation, which are then followed by adjuvant hormonal therapy. Alternatively, surgery/radiation is followed by adjuvant chemotherapy, then adjuvant hormonal therapy. IGF-1R antibodies may be administered in conjunction with the chemotherapeutic or hormonal therapy agents whether they are used either before or after surgery/radiation. Typical chemotherapy regimes for locally advanced breast cancer include FAC, AC, FEC, and doxorubicin plus docetaxel ("AT").

Metastatic breast cancer has spread to other parts of the body from the breast in which it started. Chemotherapy optionally may be preceded by hormonal therapy. First line hormonal therapy currently includes tamoxifen and anastrozole. First line chemotherapy regimens currently include FAC, TAC, docetaxel plus epirubicin, docetaxel, paclitaxel, capecitabine, vinorelbine, and trastuzumab. Second line chemotherapy treatments include docetaxel, alone or in combination with capecitabine. The methods of the present invention are suitable for use both as first line therapy and second line therapy.

In the United States, the combination of paclitaxel and carboplatin has become accepted as the standard of care for first line treatment of inoperable Stage IIIB (*i.e.* cancer has spread to structures near the lung, to lymph nodes in the mediastinum, or to lymph nodes on the other side of the chest or in the lower neck) and Stage IV (*i.e.* cancer has spread to other parts of the body or to another lobe of the lungs) non-small cell lung cancer (NSCLC). But the overall response rate is only approximately 28% for patients with performance status 0-1 in efficacy studies with a predominantly Stage IV population. In Europe, first line treatment for NSCLC is gemcitabine and cisplatin. Other treatment regimens for NSCLC include paclitaxel alone or with cisplatin or gemcitabine; docetaxel alone or with cisplatin or

gemcitabine; vinorelbine alone or with gemcitabine; irinotecan alone or with gemcitabine; pemetrexed; and gefitinib.

It is known that signaling through IGF-1R is required for the tumorgenicity of cell lines and has been shown to decrease the cytotoxicity of chemotherapy, and that blocking IGF-1R activity enhances the effectiveness of current therapies and prevents tumor progression in animal models. It was therefore expected that an inhibitor of IGF-1R such as the antibodies of the present invention would reduce tumor cell survival and enhance the efficacy of chemotherapy when given in combination.

When incubated with cells, fully human monoclonal antibodies that are highly specific and potent inhibitors of IGF-1-induced receptor autophosphorylation induced down-regulation of IGF-1R by receptor internalization. The doses that down-regulated IGF-1R in solid tumor *ex vivo* models (31.25-125 µg) corresponded to antibody concentrations of 8-40 µg/ml at Day 1 and 2-20 µg/ml at Day 9. Intraperitoneal administration of the anti-IGF-1R antibodies to athymic mice bearing tumors of the transfectant IGF-1R over-expressing NIH-3T3 cell line resulted in a dose dependent inhibition of tumor growth. The serum concentration of anti-IGF-1R antibodies that led to 50% growth inhibition was 20 µg/ml at Day 1, and 13 µg/ml at Day 9. Similar anti-tumor studies were extended to human tumor xenograft models. As a single agent, anti-IGF-1R antibodies inhibited the growth of several xenograft models including breast, lung and colorectal carcinomas.

The combination of anti-IGF-1R antibodies with paclitaxel or carboplatin was tested in the H460 and EBC-1 human NSCLC tumor xenograft models. Combination of anti-IGF-1R antibodies with those agents increased their tumor growth inhibition compared to each agent alone.

Unless otherwise defined herein, scientific, technical, and medical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry described herein are those well known and commonly used in the art.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

An "antibody" refers to an intact immunoglobulin or to an antigen-binding portion thereof that competes with the intact antibody for specific binding. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen-binding portions include, *inter alia*, Fab, Fab', $F(ab')_2$, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv),

chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

Immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk, *J. Mol. Biol.* 196:901-917 (1987); Chothia et al., *Nature* 342:878-883 (1989).

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. Examples of isolated antibodies include an anti-IGF-1R antibody that has been affinity purified using IGF-1R is an isolated antibody, an anti-IGF-1R antibody that has been synthesized by a hybridoma or other cell line *in vitro*, and a human anti-IGF-1R antibody derived from a transgenic mouse.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In a preferred embodiment, one or more of the CDRs are derived from a human anti-IGF-1R antibody. In a more preferred embodiment, all of the CDRs are derived from a human anti-IGF-1R antibody. In another preferred embodiment, the CDRs from more than one human anti-IGF-1R antibodies are mixed and matched in a chimeric antibody. Further, the framework regions may be derived from one of the same anti-IGF-1R antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody.

The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar sides chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is ≤ 1 μM, preferably ≤ 100 nM and most preferably ≤ 10 nM.

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 75% or 80% sequence identity, preferably at least 90% or 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions that are not identical differ by conservative amino acid substitutions. A

"conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, *e.g.*, Pearson, *Methods Mol. Biol.* 24: 307-31 (1994). Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; and 6) sulfur-containing side chains are cysteine and methionine. Conservative amino acids substitution groups include: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine.

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various mutations of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally-occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence).

The phrase "in combination with" encompasses simultaneous, sequential or separate dosing of the individual components of the treatment. For example, the antibody may be administered once every three days, while the additional therapeutic agent is administered once daily. The antibody may be administered prior to or subsequent to treatment of the disorder with the additional therapeutic agent. Similarly, the anti-IGF-1R antibody may be administered prior to or subsequent to other therapy, such as radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy.

The terms "concurrently" and "simultaneously" are used interchangeably and mean the compounds of the combination therapy of the present invention are administered (1) simultaneously in time, or (2) at different times during the course of a common treatment schedule. The term "sequentially" as used herein means administration of the a first

component, followed by administration of a second component. Anti-IGF-1R antibodies may be the first component or the second component. After administration of one component, the second component can be administered substantially immediately after the first component, or the second component can be administered an effective time period after the first component; the effective time period is the amount of time given for realization of maximum benefit from the administration of the first component.

The term "patient" includes mammals. In a preferred embodiment, the mammal is a human.

The term "treating," as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment," as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

Human antibodies avoid certain of the problems associated with antibodies that possess mouse or rat variable and/or constant regions. More preferred are fully human anti-human IGF-1R antibodies. Fully human anti-IGF-1R antibodies are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized monoclonal antibodies (Mabs) and thus to increase the efficacy and safety of the administered antibodies. The use of fully human antibodies can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as inflammation and cancer, which may require repeated antibody administrations. In another embodiment, the invention provides an anti-IGF-1R antibody that does not bind complement.

In another aspect of the invention, the anti-IGF-1R antibodies bind to IGF-1R with high affinity. In one embodiment, the anti-IGF-1R antibody binds to IGF-1R with a K_d of 1 x 10^{-8} M or less. In a more preferred embodiment, the antibody binds to IGF-1R with a K_d or 1 x 10^{-9} M or less. In an even more preferred embodiment, the antibody binds to IGF-1R with a K_d or 5 x 10^{-10} M or less. In another preferred embodiment, the antibody binds to IGF-1R with a K_d or 1 x 10^{-10} M or less. In another preferred embodiment, the antibody binds to IGF-1R with substantially the same K_d as an antibody selected from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the antibody binds to IGF-1R with substantially the same K_d as an antibody that comprises one or more CDRs from an antibody selected from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

The invention also employs an anti-IGF-1R antibody that binds the same antigen or epitope as a human anti-IGF-1R antibody. The invention may also employ an anti-IGF-1R antibody that cross-competes with a human anti-IGF-1R antibody. In a preferred embodiment, the human anti-IGF-1R antibody is 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or

6.1.1. In another preferred embodiment, the human anti-IGF-1R comprises one or more CDRs from an antibody selected from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1

The invention can also be practiced using an anti-IGF-1R antibody that comprises variable sequences encoded by a human κ gene. In a preferred embodiment, the variable sequences are encoded by either the Vκ A27, A30 or O12 gene family. In a preferred embodiment, the variable sequences are encoded by a human Vκ A30 gene family. In a more preferred embodiment, the light chain comprises no more than ten amino acid substitutions from the germline Vκ A27, A30 or O12, preferably no more than six amino acid substitutions, and more preferably no more than three amino acid substitutions. In a preferred embodiment, the amino acid substitutions are conservative substitutions.

In a preferred embodiment, the VL of the anti-IGF-1R antibody contains the same amino acid substitutions, relative to the germline amino acid sequence, as any one or more of the VL of antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

In another preferred embodiment, the light chain comprises an amino acid sequence that is the same as the amino acid sequence of the VL of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another highly preferred embodiment, the light chain comprises amino acid sequences that are the same as the CDR regions of the light chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the light chain comprises an amino acid sequence from at least one CDR region of the light chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

The present invention can also be carried out using an anti-IGF-1R antibody or portion thereof comprising a human heavy chain or a sequence derived from a human heavy chain. In one embodiment, the heavy chain amino acid sequence is derived from a human V_H DP-35, DP-47, DP-70, DP-71 or VIV-4/4.35 gene family. In a preferred embodiment, the heavy chain amino acid sequence is derived from a human V_H DP-47 gene family. In a more preferred embodiment, the heavy chain comprises no more than eight amino acid changes from germline V_H DP-35, DP-47, DP-70, DP-71 or VIV-4/4.35, more preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes.

In a preferred embodiment, the VH of the anti-IGF-1R antibody contains the same amino acid substitutions, relative to the germline amino acid sequence, as any one or more of the VH of antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another embodiment, the amino acid substitutions are made in the same position as those found in any one or more of the VH of antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.17.3., 4.9.2 or 6.1.1, but conservative amino acid substitutions are made rather than using the same amino acid.

In another preferred embodiment, the heavy chain comprises an amino acid sequence that is the same as the amino acid sequence of the VH of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another highly preferred embodiment, the heavy chain

comprises amino acid sequences that are the same as the CDR regions of the heavy chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the heavy chain comprises an amino acid sequence from at least one CDR region of the heavy chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the heavy chain comprises amino acid sequences from CDRs from different heavy chains. In a more preferred embodiment, the CDRs from different heavy chains are obtained from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

In another embodiment, the invention employs an anti-IGF-1R antibody that inhibits the binding of IGF-1 to IGF-1R or the binding of IGF-2 to IGF-1R. In a preferred embodiment, the IGF-1R is human. In another preferred embodiment, the anti-IGF-1R antibody is a human antibody. In another embodiment, the antibody or portion thereof inhibits binding between IGF-1R and IGF-1 with an IC_{50} of no more than 100 nM. In a preferred embodiment, the IC_{50} is no more than 10 nM. In a more preferred embodiment, the IC_{50} is no more than 5 nM. The IC_{50} can be measured by any method known in the art. Typically, an IC_{50} can be measured by ELISA or RIA. In a preferred embodiment, the IC_{50} is measured by RIA.

In another embodiment, the invention employs an anti-IGF-1R antibody that prevents activation of the IGF-1R in the presence of IGF-i. In another aspect of the invention, the antibody causes the downregulation of IGF-1R from a cell treated with the antibody. In a preferred embodiment, the antibody is selected 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, or 6.1.1, or comprises a heavy chain, light chain or antigen-binding region thereof.

Human antibodies can be produced by immunizing a non-human animal comprising of some or all of the human immunoglobulin locus with an IGF-1R antigen. In a preferred embodiment, the non-human animal is a XENOMOUSE™, which is an engineered mouse strain that comprises large fragments of the human immunoglobulin loci and is deficient in mouse antibody production. *See, e.g.*, Green et al. *Nature Genetics* 7:13-21 (1994) and United States Patent Nos. 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001, 6,114,598, and 6,130,364. *See also* International Patent Application Nos. WO 91/10741, published July 25, 1991; WO 94/02602, published February 3, 1994; WO 96/34096 and WO 96/33735, both published October 31, 1996; WO 98/16654, published April 23, 1998; WO 98/24893, published June 11, 1998; WO 98/50433, published November 12, 1998; WO 99/45031, published September 10, 1999; WO 99/53049, published October 21, 1999; WO 00/09560, published February 24, 2000; and WO 00/037504, published June 29, 2000. The XENOMOUSE ™ produces an adult-like human repertoire of fully human antibodies, and generates antigen-specific human monoclonal antibodies. A second generation XENOMOUSE™ contains approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy

chain loci and κ light chain loci. See Mendez et al. *Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998).

The IGF-1R antigen can be administered with an adjuvant to stimulate the immune response. Such adjuvants include complete or incomplete Freund's adjuvant, RIBI (muramyl dipeptides) or ISCOM (immunostimulating complexes). Such adjuvants may protect the polypeptide from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system.

The nucleic acid molecule encoding the variable region of the light chain may be derived from the A30, A27 or O12 Vκ gene. In a preferred embodiment, the light chain is derived from the A30 Vκ gene. In an even more preferred embodiment, the nucleic acid molecule encoding the light chain contains no more than ten amino acid changes from the germline A30 Vκ gene, preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes.

In one embodiment, the antibody contains no greater than ten amino acid changes in either the VH or VL regions of the mutated anti-IGF-1R antibody compared to the anti-IGF-1R antibody prior to mutation. In a more preferred embodiment, there are no more than five amino acid changes in either the VH or VL regions of the mutated anti-IGF-1R antibody, more preferably no more than three amino acid changes. In another embodiment, there are no more than fifteen amino acid changes in the constant domains, more preferably, no more than ten amino acid changes, even more preferably, no more than five amino acid changes.

SEQ ID NOS: 2, 6, 10, 14, 18 and 22 provide the amino acid sequences of the variable regions of six anti-IGF-1R κ light chains. SEQ ID NOS: 4, 8, 12, 16, 20 and 24 provide the amino acid sequences of the variable regions of six anti-IGF-1R heavy chains. SEQ ID NO: 26 depicts the amino acid sequence and SEQ ID NO: 25 depicts the nucleic acid sequence encoding the constant region of the light chain of the anti-IGF-1R antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 and 6.1.1. SEQ ID NO: 28 depicts the amino acid sequence and SEQ ID NO: 27 depicts the nucleic acid sequence encoding the constant region of the heavy chain of the anti-IGF-1R antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 and 6.1.1. SEQ ID NOS: 30, 32, 34, 36 and 44 provide the amino acid sequences of the germline heavy chains DP-35, DP-47, DP-70, DP-71 and VIV-4, respectively. SEQ ID NO: 33 provides the nucleotide sequence of the germline heavy chain DP-70. SEQ ID NOS: 38, 40 and 42 provide the amino acid sequences of the three germline κ light chains from which the six anti-IGF-1R κ light chains are derived.

The anti-IGF-1R antibodies can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically

acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion, may also be included.

The pharmaceutical compositions may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. A preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular, or infusion). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the anti-IGF-1R antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.*, Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

The pharmaceutical composition may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Dosage regimens may be adjusted to provide the optimum desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. Pharmaceutical composition comprising the antibody or comprising a combination therapy comprising the antibody and one or more additional therapeutic agents may be formulated for single or multiple doses. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. A particularly useful formulation is 5

mg/ml anti-IGF-1R antibody in a buffer of 20mM sodium citrate, pH 5.5, 140mM NaCl, and 0.2mg/ml polysorbate 80.

The antibody, with or without an additional agent, may be administered once, or more than once for at least the period of time until the condition is treated, palliated or cured. The antibody generally will be administered for as long as the tumor is present provided that the antibody causes the tumor or cancer to stop growing or to decrease in weight or volume. The antibody will generally be administered as part of a pharmaceutical composition as described *supra*. The dosage of antibody will generally be in the range of 0.025-100 mg/kg, more preferably 0.05-50 mg/kg, more preferably 0.05-20 mg/kg, and even more preferably 0.1-10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

The antibody may be administered from three times daily to once every six months. The administration may be on a schedule such as three times daily, twice daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months and once every six months. The antibody may be administered via an oral, mucosal, buccal, intranasal, inhalable, intravenous, subcutaneous, intramuscular, parenteral, intratumor or topical route.

The antibody may be administered at a site distant from the site of the tumor. The antibody may also be administered continuously via a minipump.

In certain embodiments, the antibody may be administered in an aerosol or inhalable form. Dry aerosol in the form of finely divided solid particles that are not dissolved or suspended in a liquid are also useful in the practice of the present invention. The pharmaceutical formulations of the present invention may be administered in the form of an aerosol spray using for example, a nebulizer such as those described in U.S. Patent Nos. 4,624,251; 3,703,173; 3,561,444; and 4,635,627.

The serum concentration of the antibody may be measured by any method known in the art. The antibody may also be administered prophylactically in order to prevent a cancer or tumor from occurring. This may be especially useful in patients that have a "high normal" level of IGF-1 because these patients have been shown to have a higher risk of developing common cancers. See Rosen et al., *supra.*

The antibody employed in the method of the invention can be labeled. This can be done by incorporation of a detectable marker, *e.g.*, incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin

(*e.g.*, streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain situations, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic labels (*e.g.*, horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

The antibodies employed in the present invention are preferably derived from cells that express human immunoglobulin genes. Use of transgenic mice is known in the art to produce such "human" antibodies. One such method is described in U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996. *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997); Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998); European Patent No. EP 0 463 151 (grant published June 12, 1996); and International Patent Application Nos. WO 94/02602, published February 3, 1994; WO 96/34096, published October 31, 1996; and WO 98/24893, published June 11, 1998.

As noted above, the invention encompasses use of antibody fragments. Antibody fragments, such as Fv, $F(ab')_2$ and Fab may be prepared by cleavage of the intact protein, e.g. by protease or chemical cleavage. Alternatively, a truncated gene is designed. For example, a chimeric gene encoding a portion of the $F(ab')_2$ fragment would include DNA sequences encoding the CH1 domain and hinge region of the H chain, followed by a translational stop codon to yield the truncated molecule.

In one approach, consensus sequences encoding the heavy and light chain J regions may be used to design oligonucleotides for use as primers to introduce useful restriction sites into the J region for subsequent linkage of V region segments to human C region segments. C region cDNA can be modified by site directed mutagenesis to place a restriction site at the analogous position in the human sequence.

Expression vectors for use in obtaining the antibodies employed in the invention include plasmids, retroviruses, cosmids, YACs, EBV derived episomes, and the like. A convenient vector is normally one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed. In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons.

Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The resulting chimeric antibody may be joined to any strong promoter, including retroviral LTRs, *e.g.* SV-40 early promoter (Okayama et al. *Mol. Cell. Bio.* 3:280 (1983)), Rous sarcoma virus LTR (Gorman et al. *Proc. Natl. Acad. Sci.* 79:6777 (1982)), and moloney murine leukemia virus LTR (Grosschedl et al. *Cell* 41:885 (1985)); native Ig promoters, etc.

Antibodies that are generated for use in the invention need not initially possess a particular desired isotype. Rather, the antibody as generated can possess any isotype and can be isotype switched thereafter using conventional techniques. These include direct recombinant techniques (*see e.g.*, U.S. Patent No. 4,816,397), and cell-cell fusion techniques (*see e.g.,* U.S. Patent No. 5,916,771).

As noted above, the effector function of the antibodies of the invention may be changed by isotype switching to an IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM for various therapeutic uses. Furthermore, dependence on complement for cell killing can be avoided through the use of bispecifics, immunotoxins, or radiolabels, for example.

Bispecific antibodies can be generated that comprise (i) two antibodies: one with a specificity for IGF-1R and the other for a second molecule (ii) a single antibody that has one chain specific for IGF-1R and a second chain specific for a second molecule, or (iii) a single chain antibody that has specificity for IGF-1R and the other molecule. Such bispecific antibodies can be generated using well known techniques, *e.g.,* Fanger et al. *Immunol. Methods* 4:72-81 (1994); Wright and Harris, *supra*; and Traunecker et al. *Int. J. Cancer* (Suppl.) 7:51-52 (1992).

Antibodies for use in the invention also include "kappabodies" (Ill et al. *Protein Eng.* 10:949-57 (1997)), "minibodies" (Martin et al. *EMBO J.* 13:5303-9 (1994)), "diabodies" (Holliger et al. *Proc. Natl. Acad. Sci. (USA)* 90:6444-6448 (1993)), and "janusins" (Traunecker et al. *EMBO J.* 10:3655-3659 (1991) and Traunecker et al. *Int. J. Cancer Suppl.* 7:51-52 (1992)) may also be prepared.

The antibodies employed can be modified to act as immunotoxins by conventional techniques. *See e.g.,* Vitetta *Immunol. Today* 14:252 (1993). *See also* U.S. Patent No. 5,194,594. Radiolabeled antibodies can also be prepared using well-known techniques. *See e.g.,* Junghans et al. in *Cancer Chemotherapy and Biotherapy* 655-686 (2d edition, Chafner and Longo, eds., Lippincott Raven (1996)). *See also* U.S. Patent Nos. 4,681,581, 4,735,210, 5,101,827, 5,102,990 (Re. 35,500), 5,648,471, and 5,697,902.

Particular antibodies useful in practice of the invention include those described in International Patent Application No. WO 02/053596, which further describes antibodies 2.12.1, 2.13.2., 2.14.3, 3.1.1, 4.9.2, and 4.17.3. As disclosed in that published application, hybridomas producing these antibodies were deposited in the American Type Culture

Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on December 12, 2000 with the following deposit numbers:

Hybridoma	Deposit No.
2.12.1	PTA-2792
2.13.2	PTA-2788
2.14.3	PTA-2790
3.1.1	PTA-2791
4.9.2	PTA-2789
4.17.3	PTA-2793

These antibodies are either fully human IgG2 or IgG4 heavy chains with human kappa light chains. In particular the invention concerns use of antibodies having amino acid sequences of these antibodies.

Antibodies employed in the invention preferably possess very high affinities, typically possessing Kds of from about 10^{-9} through about 10^{-11} M, when measured by either solid phase or solution phase.

Antibodies used in the present invention can be expressed in cell lines other than hybridoma cell lines. Sequences encoding the cDNAs or genomic clones for the particular antibodies can be used for transformation of suitable mammalian or nonmammalian host cells. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, particle bombardment, encapsulation of the polynucleotide(s) in liposomes, peptide conjugates, dendrimers, and direct microinjection of the DNA into nuclei.

Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, NSO_0, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), and human hepatocellular carcinoma cells (e.g., Hep G2). Non-mammalian cells can also be employed, including bacterial, yeast, insect, and plant cells. Site directed mutagenesis of the antibody CH2 domain to eliminate glycosylation may be preferred in order to prevent changes in either the immunogenicity, pharmacokinetic, and/or effector functions resulting from non-human glycosylation. The glutamine synthase system of expression is discussed in whole or part in

connection with European Patent Nos. 0 216 846, 0 256 055, and 0 323 997, and European Patent Application No. 89303964.4.

Antibodies for use in the invention can also be produced transgenically through the generation of a mammal or plant that is transgenic for the immunoglobulin heavy and light chain sequences of interest and production of the antibody in a recoverable form therefrom. Transgenic antibodies can be produced in, and recovered from, the milk of goats, cows, or other mammals. *See, e.g.,* U.S. Patent Nos. 5,827,690, 5,756,687, 5,750,172, and 5,741,957.

The advantages of the present invention can be further appreciated by reference to the following examples. These examples serve intended to illustrate preferred embodiments of the invention and are by no means intended to limit the effective scope of the claims.

EXAMPLE I:

Anti-IGF-1R Antibodies in Combination with Docetaxel in the Treatment of Advanced Non-Hematologic Malignancies

Patients with advanced-stage non-hematologic malignancies (measurable disease defined by at least one lesion that can be accurately measured and whose size is ≥2 cm x 1 cm by conventional computed tomography (CT) scan or ≥1 cm x 1 cm by spiral CT scan) received a standard dose of docetaxel (TAXOTERE) (up to 75 mg/m^2, using actual body weight to calculate body surface area (BSA)) by intravenous (IV) infusion over 1 hour on Day 1 only of each cycle. After the docetaxel infusion was completed, anti-IGF-1R antibodies as described herein were administered intravenously in a 5 mg/ml liquid formulation at a dose between 0.1 mg/kg and 10 mg/kg. The treatment regimen was repeated after 21 days, with escalation of the anti-IGF-1R antibody dose, and every 21 days thereafter until disease progression or unacceptable toxicity develops for a minimum of 2 cycles and a maximum of 17 cycles. The pre-medication regimen for docetaxel included oral dexamethasone 8 mg twice daily for three days starting one day prior to docetaxel administration. Prophylactic anti-emetics were provided as appropriate.

Dose escalation used an accelerated titration design utilizing a dose-doubling schema with 3-6 subjects per dose level (cohort). Within each new cohort there was no required waiting period between subjects. Subsequent cohorts were not opened until the first subject at the current dose level had been observed for 21 days and subsequent subjects had been observed for 14 days.

The following endpoints were measured: safety, tolerability, pharmacokinetic (PK) parameters of the anti-IGF-1R antibody; human anti-human antibody response (HAHA); response rate and time to progression; and number of circulating tumor cells (CTC) and circulating soluble IGF-1R.

EXAMPLE II:

Anti-IGF-1R Antibodies in Combination with Paclitaxel and Carboplatin in the Treatment of Advanced Non-Small Cell Lung Cancer

In Part 1 of the study, patients with Stage IIIB or Stage IV or recurrent (after surgery/radiation), measurable, non-small cell lung cancer (NSCLC) who have received no prior chemotherapy received paclitaxel (TAXOL) at a standard dose of 200 mg/m^2 by IV infusion over 3 hours. Prior to receiving paclitaxel, all patients received prophylactic anti-allergic/emetic medicines. Carboplatin (PARAPLATIN) was administered by IV infusion over 15-30 minutes; the dose was calculated based on the Calvert formula with a target area under the curve (AUC) of 6 mg/ml x min. After the carboplatin infusion was completed, anti-IGF-1R antibodies as described herein were administered intravenously in a 5 mg/ml formulation at a dose between 0.05 mg/kg and 10 mg/kg. The treatment regimen was repeated after 21 days, with escalation of the anti-IGF-1R antibody dose, and every 21 days thereafter until disease progression or unacceptable toxicity develops, for a minimum of 1 cycle and a maximum of 6 cycles.

Doses were escalated using an accelerated titration design utilizing a dose-doubling schema with 3-6 subjects per cohort. Within each new cohort there was no required waiting period between subjects. Subsequent cohorts were not opened until the first subject at the current dose level has been observed for 21 days and subsequent subjects have been observed for 14 days.

Once at least six patients have been observed for 21 days (i.e., completed one cycle), the randomized second portion of the study will begin.

Part 2 of the study is a two-arm randomized, non-comparative study of anti-IGF-1R antibody in combination with paclitaxel and carboplatin (Arm A) and of paclitaxel and carboplatin alone (Arm B). On Day 1 of Part 2, the patients in both arms are given the same dosages of paclitaxel and carboplatin, over the same time periods, as in the first part. After administration of carboplatin, patients in Arm A are also given the same anti-IGF-1R antibody dose they were given in Part 1. The dose is determined in view of the safety and tolerability demonstrated in Part 1. The treatment is repeated after 21 days, and every 21 days thereafter, until progression or unacceptable toxicity occurs for a minimum of 2 cycles and a maximum of 6.

The following endpoints are measured: PK parameters of the anti-IGF-1R antibody, HAHA, response rate and time to progression, CTC, circulating IGF-1, IGFBPs, and soluble circulating IGF-1R.

EXAMPLE III:

Anti-IGF-1R in Combination with Docetaxel and Epirubicin in Metastatic Breast Cancer

Patients having metastatic breast cancer with at least one lesion that can be accurately measured in two dimensions and whose size is ≥2 cm x 1 cm by conventional CT scan or ≥1 cm x 1 cm by spiral CT scan are given epirubicin 75 mg/m^2 as a single 15 minute infusion. After a one hour pause, docetaxel (TAXOTERE) 75 mg/m^2 is administered as a single IV infusion, followed by IV infusion of anti-IGF-1R antibodies as described herein at a dose between 0.05 mg/kg and 10 mg/kg. Prophylactic anti-emetics are given as appropriate. The treatment is repeated after 21 days with escalation of the anti-IGF-1R antibody dose, and every 21 days thereafter until disease progression or unacceptable toxicity develops for a minimum of 2 cycles and a maximum of 6.

Doses are escalated using an accelerated titration design utilizing a dose-doubling schema with 3-6 subjects per cohort. Within each new cohort there is no required waiting period between subjects. Subsequent cohorts may not be opened until the first subject at the current dose level has been observed for 21 days and subsequent subjects have been observed for 14 days.

The following endpoints are measured: PK parameters, HAHA, response rate and time to progression. Time to progression and overall survival are calculated using the Kaplan-Meier product limit method.

EXAMPLE IV: Anti-IGF-1R in Combination with Docetaxel and Prednisone in Hormone-Refractory Prostate Cancer

Subjects are patients with metastatic adenocarcinoma of the prostate who, after at least one hormonal treatment (orchiectomy, estrogens, LHRH therapy, etc.), have testosterone levels less than 50 ng/dL, prostate-specific antigen (PSA) above 20 ng/mL, and an increase in PSA > 50% over nadir value on hormonal therapy measured on 3 successive occasions at least 1 week apart. A pre-medication regimen for docetaxel includes oral dexamethasone 8 mg twice a day given for 3 days starting one day prior to docetaxel administration . A 75 mg/m^2 dose of docetaxel (TAXOTERE) (using actual body weight to calculate BSA) is administered by IV infusion over 1 hour on Day 1 only of each cycle. After the docetaxel infusion is completed, anti-IGF-1R antibodies as described herein are administered intravenously in a 5 mg/ml liquid formulation. Prednisone is given daily in two oral 5 mg doses per day, starting on Day 1. Prophylactic anti-emetics may be given as appropriate. The treatment regimen is repeated every 21 days (±3 days) until disease progression or unacceptable toxicity develops, for a maximum of 10 cycles.

The following endpoints are measured: PSA response, population PK parameters of the anti-IGF-1R antibody, HAHA, total number of CTCs and CTCs expressing IGF-1R.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

1. A method for the treatment of a non-hematologic malignancy in a patient in need of such treatment comprising the step of administering to the patient a therapeutically effective amount of an antibody that specifically binds to IGF-1R in combination with a therapeutically effective amount of at least one agent selected from the group consisting of an alkylating agent, a folate antagonist, a pyrimidine antagonist, a cytotoxic antibiotic, a platinum compound, a taxane, a vinca alkaloid, a topoisomerase inhibitor, an EGFR inhibitor, and a hormonal therapy agent.

2. The method of claim 1, wherein the agent is a taxane.

3. The method of claim 2, wherein the taxane is docetaxel.

4. The method of claim 2, wherein the taxane is paclitaxel.

5. The method of any one of claims 3 and 4, wherein the antibody and the taxane are administered in combination with an additional therapeutic agent selected from the group consisting of carboplatin, cisplatin, gemcitabine, capecitabine, epirubicin and prednisone.

6. The method of claim 5, wherein the additional therapeutic agent is carboplatin.

7. The method of claim 5, wherein the additional therapeutic agent is epirubicin.

8. The method of claim 5, wherein the additional therapeutic agent is prednisone.

9. The method of any one of claims 1-8, wherein the non-hematological malignancy is breast cancer.

10. The method of any one of claims 1-8, wherein the non-hematological malignancy is lung cancer.

11. The method of any one of claims 1-8, wherein the non-hematological malignancy is prostate cancer.

12. A pharmaceutical composition for the treatment of a non-hematologic malignancy according to the method of any one of claims 1-11, comprising:

a therapeutically effective amount of an antibody that specifically binds IGF-1R,

a therapeutically effective amount of at least one agent selected from the group consisting of an alkylating agent, a folate antagonist, a pyrimidine antagonist, a cytotoxic antibiotic, a platinum compound, a taxane, a vinca alkaloid, a topoisomerase inhibitor, an EGFR inhibitor, and a hormonal therapy agent; and

a pharmaceutically acceptable carrier.

13. The composition of claim 12 wherein the antibody has the following properties:

a binding affinity for human IGF-1R of K_d of 8×10^{-9} or less; and

inhibition of binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100 nM.

14. The composition of any one of claims 12 or 13 wherein the antibody comprises at least one of the group consisting of:

(a) a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3 of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1;

(b) a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3 of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1; and

(c) sequences having changes from the CDR sequences of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1, said sequences being selected from the group consisting of conservative changes, wherein the conservative changes are selected from the group consisting of replacement of nonpolar residues by other nonpolar residues, replacement of polar charged residues by other polar uncharged residues, replacement of polar charged residues by other polar charged residues, and substitution of structurally similar residues; and non-conservative substitutions, wherein the non-conservative substitutions are selected from the group consisting of substitution of polar charged residue for polar uncharged residues and substitution of nonpolar residues for polar residues, additions and deletions.

15. The composition of any one of claims 12-14, wherein the antibody comprises a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, and a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1.

16. The composition of any one of claims 12-15, wherein the antibody is selected from the group consisting of an antibody comprising a heavy chain amino acid sequence derived from human gene DP-47 and a light chain amino acid sequence derived from human gene A30.

FIG. 1A

```
2.13.2K    GACATCCAGA TGACCCAGTT TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
A30        GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
2.14.3k    ---------- ---------- ----TCCTCC CTGTCTGCAT CTGTAGGAGA  26
2.12.1k    ---------- ---------- ---------- -----TGCAT CTGTAGGAGA  15
4.9.2k     GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
Consensus  GACATCCAGA TGACCCAGTY TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
                                                    CDR1

2.13.2K    CAGAGTCACC ATCACTTGCC GGGCAAGTCA GGGCATTAGA AATGATTTAG 100
A30        CAGAGTCACC ATCACTTGCC GGGCAAGTCA GGGCATTAGA AATGATTTAG 100
2.14.3k    CAGAGTCACC TTCACTTGCC GGGCAAGTCA GGACATTAGA CGTGATTTAG  76
2.12.1k    CAGAGTCACC TTCACTTGCC GGGCAAGTCA GGACATTAGA CGTGATTTAG  65
4.9.2k     CAGAGTCACC ATCACTTGCC GGGCAAGTCA GGGCATTAGA AGTGATTTAG 100
Consensus  CAGAGTCACC WTCACTTGCC GGGCAAGTCA GGRCATTAGA MRTGATTTAG 100

2.13.2K    GCTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCGCCT GATCTATGCT 150
A30        GCTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCGCCT GATCTATGCT 150
2.14.3k    GCTGGTATCA GCAGAAACCA GGGAAAGCTC CTAAGCGCCT GATCTATGCT 126
2.12.1k    GCTGGTATCA GCAGAAACCA GGGAAAGCTC CTAAGCGCCT GATCTATGCT 115
4.9.2k     GCTGGTTTCA GCAGAAACCA GGGAAAGCCC CTAAGCGCCT GATCTATGCT 150
Consensus  GCTGGTWTCA GCAGAAACCA GGGAAAGCYC CTAAGCGCCT GATCTATGCT 150
           CDR2

2.13.2K    GCATCCCGTT TGCACAGAGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 200
A30        GCATCCAGTT TGCAAAGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 200
2.14.3k    GCATCCCGTT TACAAAGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 176
2.12.1k    GCATCCCGTT TACAAAGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 165
4.9.2k     GCATCCAAAT TACACCGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 200
Consensus  GCATCCMRWT TRCAMMGWGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 200

2.13.2K    TGGGACAGAA TTCACTCTCA CAATCAGCAG CCTGCAGCCT GAAGATTTTG 250
A30        TGGGACAGAA TTCACTCTCA CAATCAGCAG CCTGCAGCCT GAAGATTTTG 250
2.14.3k    TGGGACAGAA TTCACTCTCA CAATCAGCAG CCTGCAGCCT GAAGATTTTG 226
2.12.1k    TGGGACAGAA TTCACTCTCA CAATCAGCAG CCTGCAGCCT GAAGATTTTG 215
4.9.2k     TGGGACAGAA TTCACTCTCA CAATCAGCCG CCTGCAGCCT GAAGATTTTG 250
Consensus  TGGGACAGAA TTCACTCTCA CAATCAGCMG CCTGCAGCCT GAAGATTTTG 250
                                                    CDR3

2.13.2K    CAACTTATTA CTGTTTACAA CATAATAGTT ACCCGTGCAG TTTTGGCCAG 300
A30        CAACTTATTA CTGTCTACAG CATAATAGTT ACCC-TCCN- ---------- 288
2.14.3k    CAACTTATTA CTGTCTACAG CATAATAATT ATCCTCGGAC GTTCGGCCAA 276
2.12.1k    CAACTTATTA CTGTCTACAG CATAATAATT ATCCTCGGAC GTTCGGCCAA 265
4.9.2k     CAACTTATTA CTGTCTACAG CATAATAGTT ACCCTCGGAC TTTCGGCGGA 300
Consensus  CAACTTATTA CTGTYTACAR CATAATARTT AYCCKYBSNS KTTYGGCSRR 300

2.13.2K    GGGACCAAGC TGGAGATCAA AC----                          322
A30        ---------- ---------- ------                          288
2.14.3k    GGGACCAAGC TGGAAATCAT ACGAAC                          302
2.12.1k    GGGACCAAGC TGGAAATCAT ACGAAC                          291
4.9.2k     GGGACCAAGC TGGAGATCAA AC----                          322
Consensus  GGGACCRAGS TGGARATCAW ACGAAC                          326
```

FIG. 1B

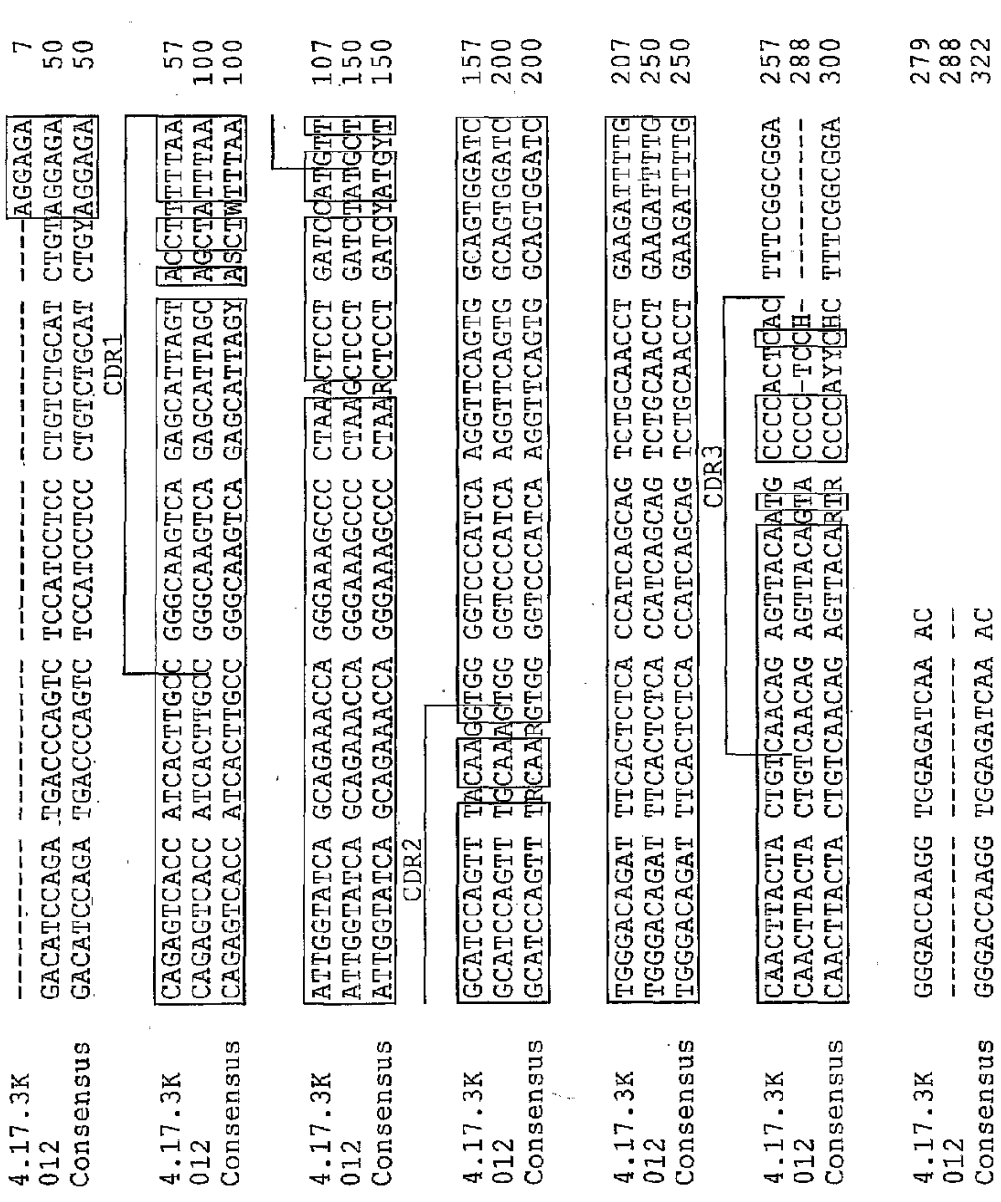
4.17.3K ---------- ---------- ---------- ---------- ---AGGAGA 7
012 GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA 50
Consensus GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGYAGGAGA 50
CDR1
4.17.3K CAGAGTCACC ATCACTTGCC GGGCAAGTCA GAGCATTAGT ACCTTTTTAA 57
012 CAGAGTCACC ATCACTTGCC GGGCAAGTCA GAGCATTAGC AGCTATTTAA 100
Consensus CAGAGTCACC ATCACTTGCC GGGCAAGTCA GAGCATTAGY ASCTWTTTAA 100
4.17.3K ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAACTCCT GATCCATGTT 107
012 ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATGCT 150
Consensus ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAARCTCCT GATCYATGYT 150
CDR2
4.17.3K GCATCCAGTT TACAAGGTGG GGTCCCATCA AGGTTCAGTG GCAGTGGATC 157
012 GCATCCAGTT TGCAAAGTGG GGTCCCATCA AGGTTCAGTG GCAGTGGATC 200
Consensus GCATCCAGTT TRCAARGTGG GGTCCCATCA AGGTTCAGTG GCAGTGGATC 200
4.17.3K TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG 207
012 TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG 250
Consensus TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG 250
CDR3
4.17.3K CAACTTACTA CTGTCAACAG AGTTACAATG CCCCACTCAC TTTCGGCGGA 257
012 CAACTTACTA CTGTCAACAG AGTTACAGTA CCCC-TCCH- ---------- 288
Consensus CAACTTACTA CTGTCAACAG AGTTACARTR CCCCAYYCHC TTTCGGCGGA 300
4.17.3K GGGACCAAGG TGGAGATCAA AC 279
012 ---------- ---------- -- 288
Consensus GGGACCAAGG TGGAGATCAA AC 322

FIG. 1C

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6.1.1K      ---------- ---------- ---------- ---------- ----------
A27         GAAATTGTGT TGACGCAGTC TCCAGGCACC CTGTCTTTGT GTCCAGGGGA   50
Consensus   GAAATTGTGT TGACGCAGTC TCCAGGCACC CTGTCTTTGT GTCCAGGGGA   50
                                        CDR1
6.1.1K      -AGAGCCACC CTCTCCTGTA GGGCCAGTCA GAGTGTTCGC GGCAGGTACT   49
A27         AAGAGCCACC CTCTCCTGCA GGGCCAGTCA GAGTGTTAGC AGCAGCTACT  100
Consensus   AAGAGCCACC CTCTCCTGYA GGGCCAGTCA GAGTGTTMGC RGCAGSTACT  100

6.1.1K      TAGCCTGGTA CCAGCAGAAA CCTGGCCAGG CTCCCAGGCT CCTCATCTAT   99
A27         TAGCCTGGTA CCAGCAGAAA CCTGGCCAGG CTCCCAGGCT CCTCATCTAT  150
Consensus   TAGCCTGGTA CCAGCAGAAA CCTGGCCAGG CTCCCAGGCT CCTCATCTAT  150
                  CDR2
6.1.1K      GGTGCATCCA GCAGGGCCAC TGGCATCCCA GACAGGTTCA GTGGCAGTGG  149
A27         GGTGCATCCA GCAGGGCCAC TGGCATCCCA GACAGGTTCA GTGGCAGTGG  200
Consensus   GGTGCATCCA GCAGGGCCAC TGGCATCCCA GACAGGTTCA GTGGCAGTGG  200

6.1.1K      GTCTGGGACA GACTTCACTC TCACCATCAG CAGACTGGAG CCTGAAGATT  199
A27         GTCTGGGACA GACTTCACTC TCACCATCAG CAGACTGGAG CCTGAAGATT  250
Consensus   GTCTGGGACA GACTTCACTC TCACCATCAG CAGACTGGAG CCTGAAGATT  250
                                        CDR3
6.1.1K      TTGCAGTGTT TTACTGTCAG CAGTATGGTA GTTCACCTCG NACGTTCGGC  249
A27         TTGCAGTGTA TTACTGTCAG CAGTATGGTA GCTCACCTCC ----------  288
Consensus   TTGCAGTGTW TTACTGTCAG CAGTATGGTA GYTCACCTCS NACGTTCGGC  300

6.1.1K      CAAGGGACCA AGGTGGAAAT CAAAC                            274
A27         ---------- ---------- -----                            290
Consensus   CAAGGGACCA AGGTGGAAAT CAAAC                            325
```

FIG. 2A

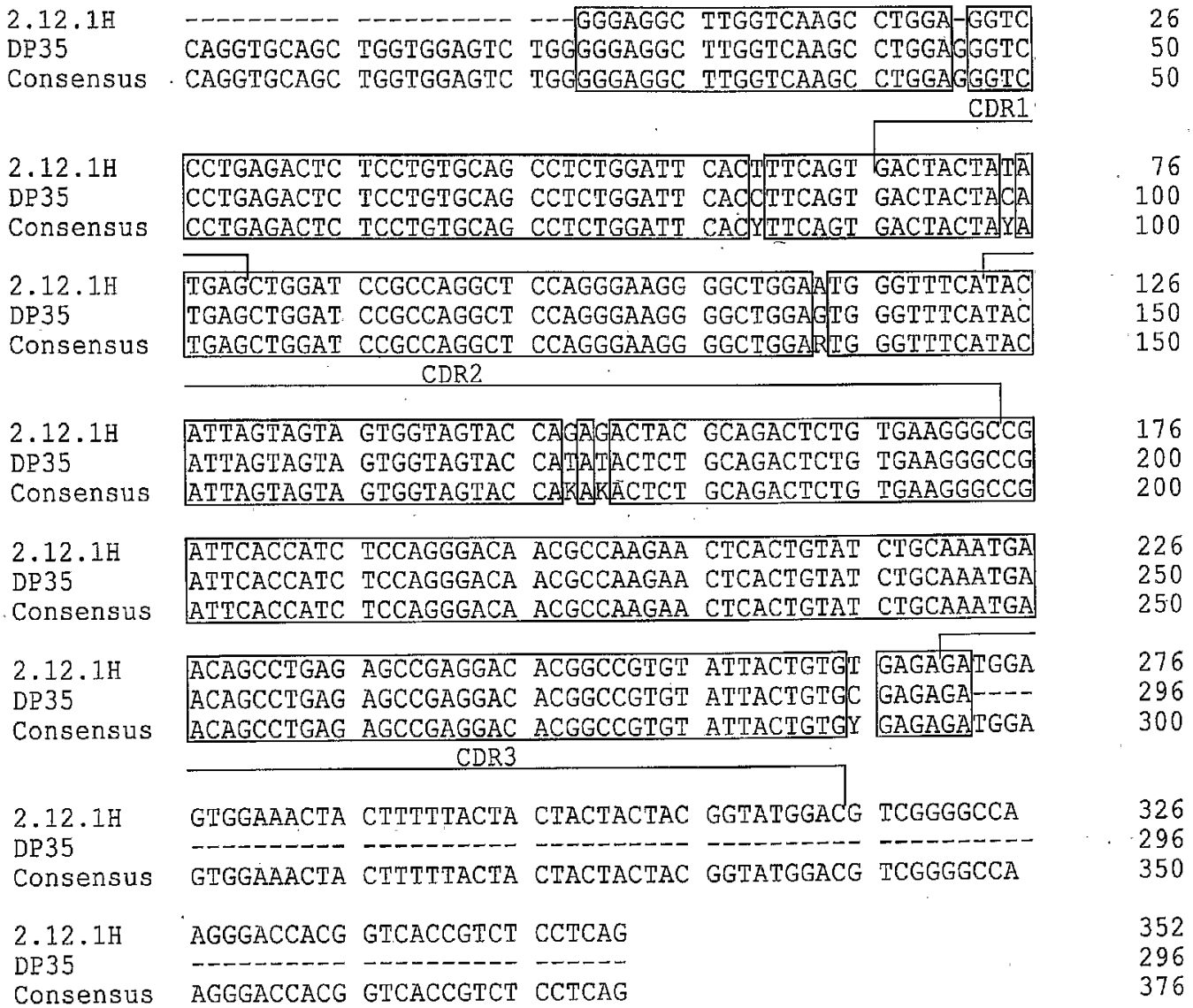

2.12.1H ---------- ---------- ---GGGAGGC TTGGTCAAGC CTGGA-GGTC 26
DP35 CAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCAAGC CTGGAGGGTC 50
Consensus CAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCAAGC CTGGAGGGTC 50
CDR1
2.12.1H CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACTTTCAGT GACTACTATA 76
DP35 CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTCAGT GACTACTACA 100
Consensus CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACYTTCAGT GACTACTAYA 100
2.12.1H TGAGCTGGAT CCGCCAGGCT CCAGGGAAGG GGCTGGAATG GGTTTCATAC 126
DP35 TGAGCTGGAT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTTTCATAC 150
Consensus TGAGCTGGAT CCGCCAGGCT CCAGGGAAGG GGCTGGARTG GGTTTCATAC 150
CDR2
2.12.1H ATTAGTAGTA GTGGTAGTAC CAGAGACTAC GCAGACTCTG TGAAGGGCCG 176
DP35 ATTAGTAGTA GTGGTAGTAC CATATACTCT GCAGACTCTG TGAAGGGCCG 200
Consensus ATTAGTAGTA GTGGTAGTAC CAKAKACTCT GCAGACTCTG TGAAGGGCCG 200
2.12.1H ATTCACCATC TCCAGGGACA ACGCCAAGAA CTCACTGTAT CTGCAAATGA 226
DP35 ATTCACCATC TCCAGGGACA ACGCCAAGAA CTCACTGTAT CTGCAAATGA 250
Consensus ATTCACCATC TCCAGGGACA ACGCCAAGAA CTCACTGTAT CTGCAAATGA 250
2.12.1H ACAGCCTGAG AGCCGAGGAC ACGGCCGTGT ATTACTGTGT GAGAGATGGA 276
DP35 ACAGCCTGAG AGCCGAGGAC ACGGCCGTGT ATTACTGTGC GAGAGA---- 296
Consensus ACAGCCTGAG AGCCGAGGAC ACGGCCGTGT ATTACTGTGY GAGAGATGGA 300
CDR3
2.12.1H GTGGAAACTA CTTTTTACTA CTACTACTAC GGTATGGACG TCGGGGCCA 326
DP35 ---------- ---------- ---------- ---------- ---------- 296
Consensus GTGGAAACTA CTTTTTACTA CTACTACTAC GGTATGGACG TCGGGGCCA 350
2.12.1H AGGGACCACG GTCACCGTCT CCTCAG 352
DP35 ---------- ---------- ------ 296
Consensus AGGGACCACG GTCACCGTCT CCTCAG 376

FIG. 2B

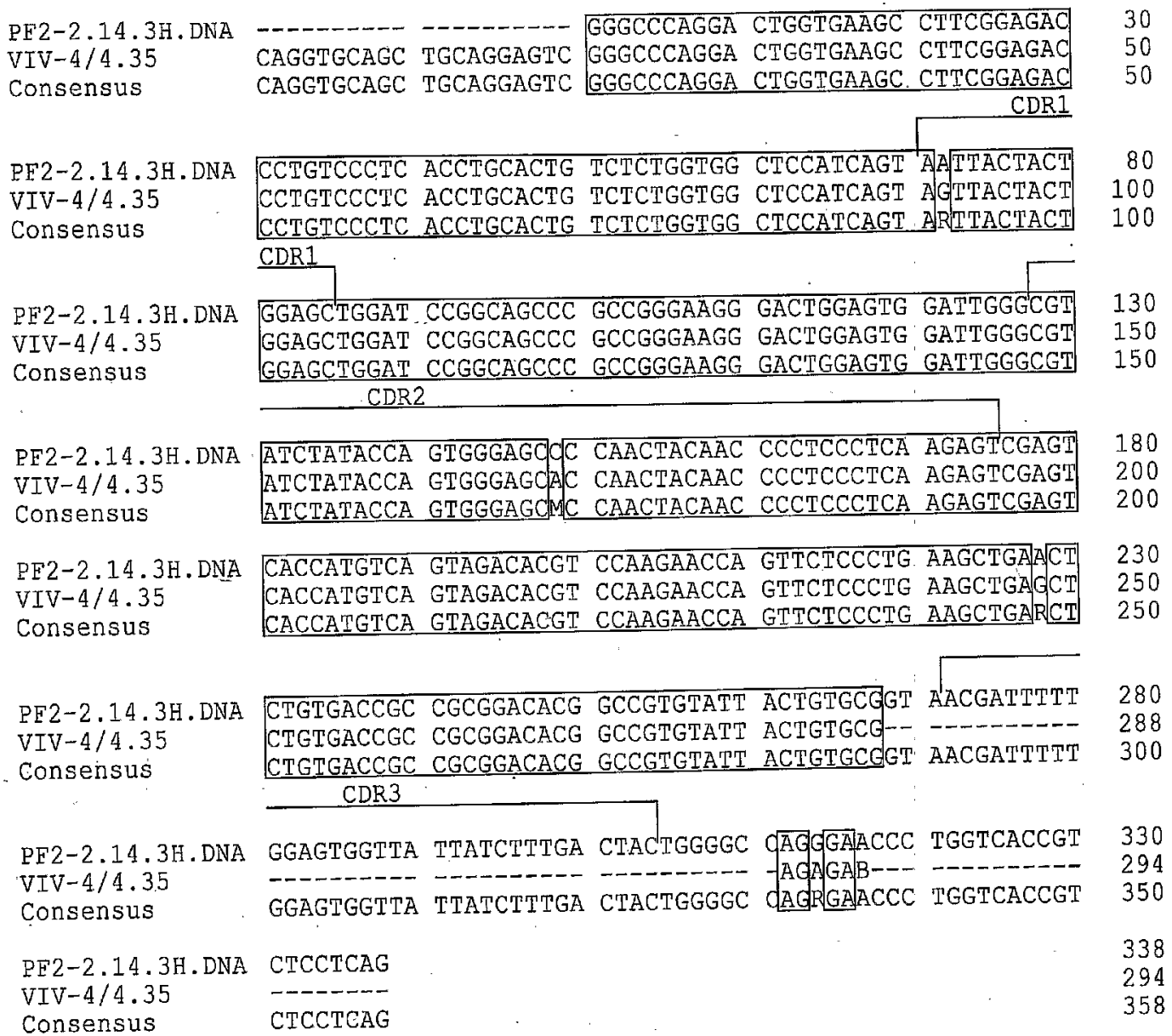
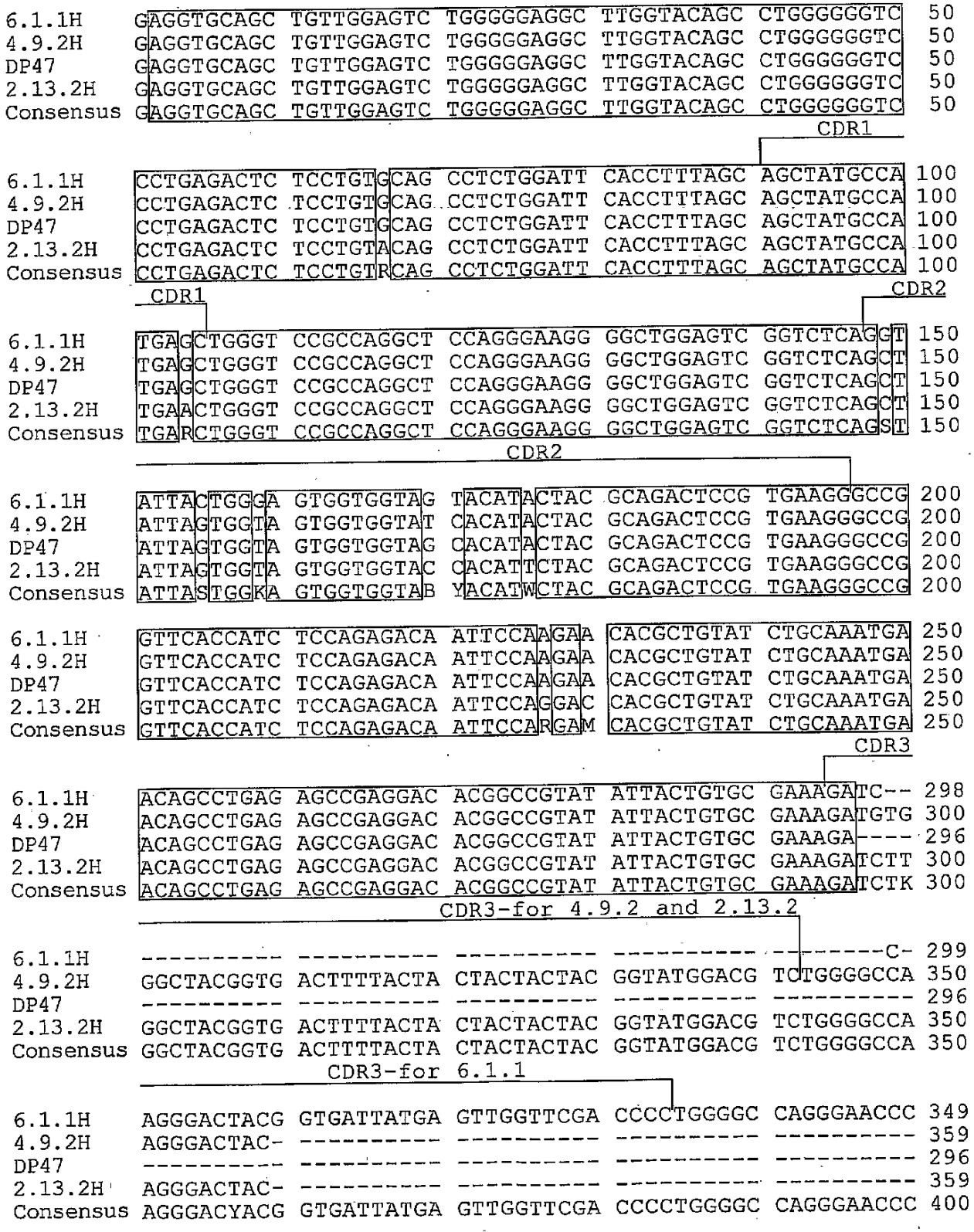

PF2-2.14.3H.DNA ---------- ---------- GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC 30
VIV-4/4.35 CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC 50
Consensus CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC 50
CDR1
PF2-2.14.3H.DNA CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AATTACTACT 80
VIV-4/4.35 CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT 100
Consensus CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT ARTTACTACT 100
CDR1
PF2-2.14.3H.DNA GGAGCTGGAT CCGGCAGCCC GCCGGGAAGG GACTGGAGTG GATTGGGCGT 130
VIV-4/4.35 GGAGCTGGAT CCGGCAGCCC GCCGGGAAGG GACTGGAGTG GATTGGGCGT 150
Consensus GGAGCTGGAT CCGGCAGCCC GCCGGGAAGG GACTGGAGTG GATTGGGCGT 150
CDR2
PF2-2.14.3H.DNA ATCTATACCA GTGGGAGCCC CAACTACAAC CCCTCCCTCA AGAGTCGAGT 180
VIV-4/4.35 ATCTATACCA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT 200
Consensus ATCTATACCA GTGGGAGCMC CAACTACAAC CCCTCCCTCA AGAGTCGAGT 200
PF2-2.14.3H.DNA CACCATGTCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAACT 230
VIV-4/4.35 CACCATGTCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGCT 250
Consensus CACCATGTCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGARCT 250
PF2-2.14.3H.DNA CTGTGACCGC CGCGGACACG GCCGTGTATT ACTGTGCGGT AACGATTTTT 280
VIV-4/4.35 CTGTGACCGC CGCGGACACG GCCGTGTATT ACTGTGCG-- ---------- 288
Consensus CTGTGACCGC CGCGGACACG GCCGTGTATT ACTGTGCGGT AACGATTTTT 300
CDR3
PF2-2.14.3H.DNA GGAGTGGTTA TTATCTTTGA CTACTGGGGC CAGGGAACCC TGGTCACCGT 330
VIV-4/4.35 ---------- ---------- ---------- -AGAGAB--- ---------- 294
Consensus GGAGTGGTTA TTATCTTTGA CTACTGGGGC CAGRGAACCC TGGTCACCGT 350
PF2-2.14.3H.DNA CTCCTCAG 338
VIV-4/4.35 -------- 294
Consensus CTCCTCAG 358

FIG. 2C-1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4.9.2H GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC 50
DP47 GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC 50
2.13.2H GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC 50
Consensus GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC 50
CDR1
6.1.1H CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
4.9.2H CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
DP47 CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
2.13.2H CCTGAGACTC TCCTGTACAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
Consensus CCTGAGACTC TCCTGTRCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
CDR1
CDR2
6.1.1H TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGGT 150
4.9.2H TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGCT 150
DP47 TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGCT 150
2.13.2H TGAACTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGCT 150
Consensus TGARCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGST 150
CDR2
6.1.1H ATTACTGGGA GTGGTGGTAG TACATACTAC GCAGACTCCG TGAAGGGCCG 200
4.9.2H ATTAGTGGTA GTGGTGGTAT CACATACTAC GCAGACTCCG TGAAGGGCCG 200
DP47 ATTAGTGGTA GTGGTGGTAG CACATACTAC GCAGACTCCG TGAAGGGCCG 200
2.13.2H ATTAGTGGTA GTGGTGGTAC CACATTCTAC GCAGACTCCG TGAAGGGCCG 200
Consensus ATTASTGGKA GTGGTGGTAB YACATWCTAC GCAGACTCCG TGAAGGGCCG 200
6.1.1H GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CTGCAAATGA 250
4.9.2H GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CTGCAAATGA 250
DP47 GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CTGCAAATGA 250
2.13.2H GTTCACCATC TCCAGAGACA ATTCCAGGAC CACGCTGTAT CTGCAAATGA 250
Consensus GTTCACCATC TCCAGAGACA ATTCCARGAM CACGCTGTAT CTGCAAATGA 250
CDR3
6.1.1H ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATC-- 298
4.9.2H ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATGTG 300
DP47 ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGA---- 296
2.13.2H ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATCTT 300
Consensus ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATCTK 300
CDR3-for 4.9.2 and 2.13.2
6.1.1H ---------- ---------- ---------- ----------C- 299
4.9.2H GGCTACGGTG ACTTTTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA 350
DP47 ---------- ---------- ---------- ---------- ---------- 296
2.13.2H GGCTACGGTG ACTTTTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA 350
Consensus GGCTACGGTG ACTTTTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA 350
CDR3-for 6.1.1
6.1.1H AGGGACTACG GTGATTATGA GTTGGTTCGA CCCCTGGGGC CAGGGAACCC 349
4.9.2H AGGGACTAC- ---------- ---------- ---------- ---------- 359
DP47 ---------- ---------- ---------- ---------- ---------- 296
2.13.2H AGGGACTAC- ---------- ---------- ---------- ---------- 359
Consensus AGGGACYACG GTGATTATGA GTTGGTTCGA CCCCTGGGGC CAGGGAACCC 400

FIG. 2C-2

```
6.1.1H     TGGTCACCGT CTCCTCAG                                        367
4.9.2H     -GGTCACCGT CTCCTCAG                                        376
DP47       ---------- --------                                        296
2.13.2H    -GGTCACCGT CTCCTCAG                                        376
Consensus  TGGTCACCGT CTCCTCAG                                        418
```

FIG. 2D

```
4.17.3H    ---------- ---------- ---CCCAGGA CTGGTGAAGC CTTCGGAGAC   27
DP71       CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC   50
Consensus  CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC   50
                                                          CDR1

4.17.3H    CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT   77
DP71       CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT  100
Consensus  CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT  100
           CDR1

4.17.3H    GGAGTTGGAT CCGGCAGCCC CCAGGGAAGG GACTGGAGTG GATTGGGTAT  127
DP71       GGAGCTGGAT CCGGCAGCCC CCAGGGAAGG GACTGGAGTG GATTGGGTAT  150
Consensus  GGAGYTGGAT CCGGCAGCCC CCAGGGAAGG GACTGGAGTG GATTGGGTAT  150
                  CDR2

4.17.3H    ATCTATTACA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT  177
DP71       ATCTATTACA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT  200
Consensus  ATCTATTACA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT  200

4.17.3H    CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGTT  227
DP71       CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGCT  250
Consensus  CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGYT  250
                                CDR3

4.17.3H    CTGTGACCGC TGCGGACACG GCCGTGTATT ACTGTGCCAG GACGTATAGC  277
DP71       CTGTGACCGC TGCGGACACG GCCGTGTATT ACTGTGC--- GA--------  289
Consensus  CTGTGACCGC TGCGGACACG GCCGTGTATT ACTGTGCCAG GACGTATAGC  300

4.17.3H    AGTTCGTTCT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  327
DP71       ---------- ---------- ----GA---- ---------- -GA-------  293
Consensus  AGTTCGTTCT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  350

4.17.3H    CACCGTCTCC TCAG                                        341
DP71       ---------- ----                                        293
Consensus  CACCGTCTCC TCAG                                        364
```

FIG. 3A

Clone	C domain mutations	FR mutation	CDR mutation	Change in Cys	Change in glycosylation
2.13.2 Heavy	0	3	8	0	0
2.13.2 Light	0	1	4	1 (CDR3)	0
2.12.2 Heavy	0	2	8	0	0
2.12.2 Light	0	3	5	0	0

FIG. 3B

PF2 2.13.2 Heavy chain (DP-47 (3-23)/D6-19/JH6)

```
                                                +         *                   * *                 ++
MEFGLSWLFL VAILKGVQCE VQLLZSGGGL VQPGGSLRLS CTASGFTFSS YAMNWVRQAP GKGLEWVSAI SGSGGTTFYA DSVKGRFTIS RDNSRTTLYL
MEFGLSWLFL VAILKGVQCE VQLLZSGGGL VQPGGSLRLS CAASGFTFSS YAMSWVRQAP GKGLEWVSAI SGSGGTTFYA DSVKGRFTIS RDNSRTTLYL
                      * *  ***

QMNSLRAEDT AVYYCAK--D LGWSDSYYYY YGMDVWGQGT TVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP
QMNSLRAEDT AVYYCAKGYS SGW--YYYYY YGMDVWGQGT TVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP

AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVQF
AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVQF

NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS
NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS

DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
```

FIG. 3C

PF2 2.13.2 LC (A30/Jk2)

```
                                +                                                   * *
MDMRVPAQLL GLLLLWFPGA RCDIQMTQFP SSLSASVGDR VTITCRASQG IRNDLGWYQQ KPGKAPKRLI YAASRLHRGV PSRFSGSGSG TEFTLTISSL
DMRVPAQLLL GLLLLWFPGA RCDIQMTQSP SSLSASVGDR VTITCRASQG IRNDLGWYQQ KPGKAPKRLI YAASSLQSGV PSRFSGSGSG TEFTLTISSL
                  **
QPEDFATYYC LQHNSYPCSF GQGTKLEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
QPEDFATYYC LQHNSYPYTF GQGTKLEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST

LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

FIG. 3D

PF2 2.12.1 Heavy chain (DP-35-(3-11)/D3-3/JH6)

```
                      +                                                          **
MEFGLSWVFL VAIIKGVQCQ AQLVESGGGL VKPGGSLRLS CAASGFTFSD YYMSWIRQAP GKGLEWVSYI SSSGSTRDYA DSVKGRFTIS RDNAKNSLYL
MEFGLSWVFL VAIIKGVQCQ VQLVESGGGL VKPGGSLRLS CAASGFTFSD YYMSWIRQAP GKGLEWVSYI SSSGSTIYYA DSVKGRFTIS RDNAKNSLYL
                   +   * ** ***
QMNSLRAEDT AVYYCVR--D GVETTF-YYY YYGMDVWGQG TTVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF
QMNSLRAEDT AVYYCARVLR GVETTFYYYY YYGMDVWGQG TTVTVSSAST KGPSVFPLAP CSRSTSESTA ALOCLVKDYF PEPVTVSWNS CALTSGVHTF

PAVLQSSGLY SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ
PAVLQSSGLY SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ

PNWYVDGVEV HNAKTKPREE QFNSTFRVVS VLTVVHQDWL NGKEYKCKVS NKGLPAPIEK TISKTKGQPRE PQVYTLPPS REEMTKNQVS LTCLVKGFYP
PNWYVDGVEV HNAKTKPREE QFNSTFRVVS VLTVVHQDWL NGKEYKCKVS NKGLPAPIEK TISKTKGQPRE PQVYTLPPS REEMTKNQVS LTCLVKGFYP

SDIAVEWESN GQPENNYKTT PPMLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLSP GK
SDIAVEWESN GQPENNYKTT PPMLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLSP GK
```

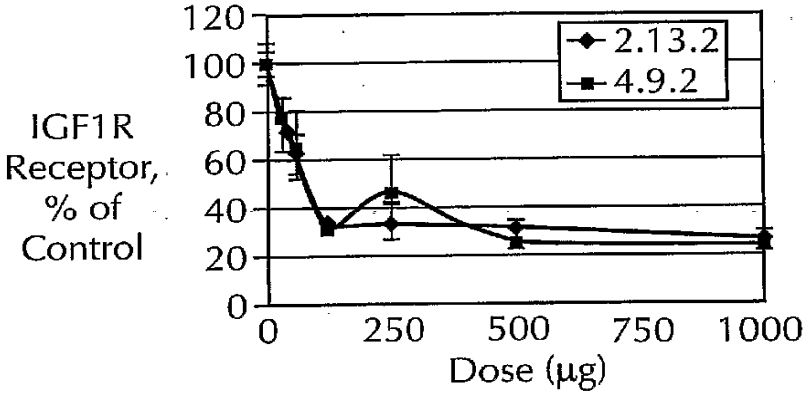
FIG. 3E

PF2.12.1 Light chain. (A30/JK1)

```
                                                +     *   *                       *
MDMRVPAQLL GLLLLWFPGA RCDIQMTQSP SSLSASVGDR VTFTCRASQD IRRDLGWYQQ KPGKAPKRLI YAASRLQSGV PSRFSGSGSG TEFTLTISSL
MDMRVPAQLL GLLLLWFPGA RCDIQMTQSP SSLSASVGDR VTFTCRASQD IRRDLGWYQQ KPGKAPKRLI YAASRLQSGV PSRFSGSGSG TEFTLTISSL
                          +   +
QPEDFATYYC LQHNNYPRTF GQGTEVEIIR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
QPEDFATYYC LQHNNYPRTF GQGTEVEIIR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST

LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

FIG. 4


IGF1R Receptor, % of Control
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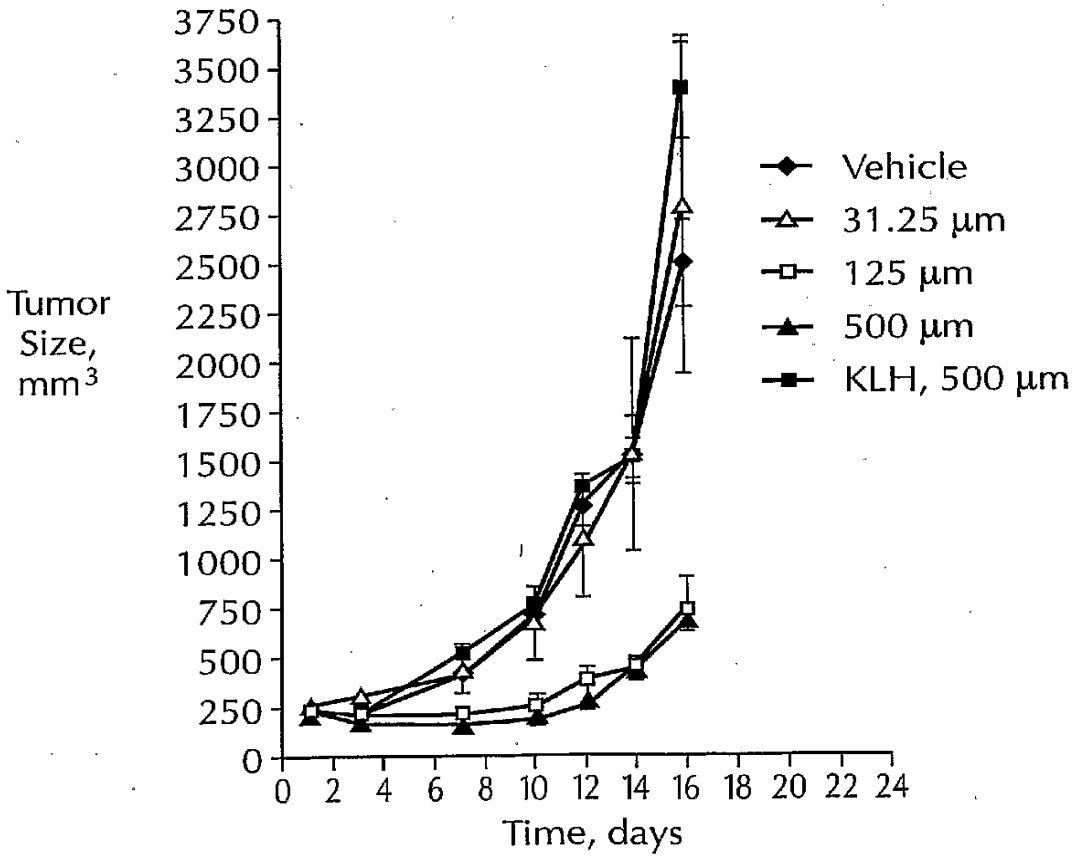
100
80
60
40
20
0
0
250
500
750
1000
Dose (µg)
2.13.2
4.9.2

FIG. 5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3500
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3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time, days
Vehicle
31.25 µm
125 µm
500 µm
KLH, 500 µm

PC32226A.ST25
SEQUENCE LISTING

<110> Cohen, Bruce
Gualberto, Antonio
Melvin, Carrie
Roberts, Luisa M.

<120> COMBINATION TREATMENT FOR BREAST CANCER

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<151> 2004-07-16

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ccgtttacaa agtggggtcc catcaaggtt cagcggcagt ggatctggga cagaattcac 180

tctcacaatc agcagcctgc agcctgaaga ttttgcaact tattactgtc tacagcataa 240

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20 25 30

Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
35 40 45

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
50 55 60

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn
65 70 75 80

Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val Glu Ile Ile Arg

85 90 95

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
100 105 110

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115 120 125

Pro Arg Glu Ala Lys Val Gln Trp
130 135

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tcatacatta gtagtagtgg tagtaccaga gactacgcag actctgtgaa gggccgattc 180

accatctcca gggacaacgc caagaactca ctgtatctgc aaatgaacag cctgagagcc 240

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20 25 30

Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser
35 40 45

Thr Arg Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
50 55 60

Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
65 70 75 80

Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg Asp Gly Val Glu Thr Thr
85 90 95

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```
Phe Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

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gggaaagccc ctaagcgcct gatctatgct gcatcccgtt tgcacagagg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

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            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Arg Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
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cagggaaggg gctggagtgg gtctcagcta ttagtggtag tggtggtacc acattctacg 180

cagactccgt gaagggccgg ttcaccatct ccagagacaa ttccaggacc acgctgtatc 240

tgcaaatgaa cagcctgaga gccgaggaca cggccgtata ttactgtgcg aaagatcttg 300

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20 25 30

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35 40 45

Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

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tatgctgcat cccgtttaca aagtggggtc ccatcaaggt tcagcggcag tggatctggg 180

acagaattca ctctcacaat cagcagcctg cagcctgaag attttgcaac ttattactgt 240

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1 5 10 15

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20 25 30

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35 40 45

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
50 55 60

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
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Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr
1 5 10 15

Val Ser Gly Gly Ser Ile Ser Asn Tyr Tyr Trp Ser Trp Ile Arg Gln
20 25 30

Pro Ala Gly Lys Gly Leu Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly
35 40 45

Ser Pro Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met Ser Val
50 55 60

Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Asn Ser Val Thr Ala
65 70 75 80

Ala Asp Thr Ala Val Tyr Tyr Cys Ala Val Thr Ile Phe Gly Val Val
85 90 95

Ile Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 13
<211> 322
<212> DNA
<213> Homo sapiens

<400> 13
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga agtgatttag gctggtttca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccaaat tacaccgtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagccg cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataatagtt accctctcac tttcggcgga 300

gggaccaagg tggagatcaa ac 322

<210> 14
<211> 107
<212> PRT
<213> Homo sapiens

<400> 14

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ser Asp
20 25 30

Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Lys Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Arg Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 15
<211> 376
<212> DNA
<213> Homo sapiens

<400> 15
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtat cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatctg 300

ggctacggtg acttttacta ctactactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctcag 376

<210> 16
<211> 125
<212> PRT
<213> Homo sapiens

<400> 16

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ile Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu Gly Tyr Gly Asp Phe Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 17
<211> 279
<212> DNA
<213> Homo sapiens

<400> 17
caggagacag agtcaccatc acttgccggg caagtcagag cattagtacc tttttaaatt 60

ggtatcagca gaaaccaggg aaagccccta aactcctgat ccatgttgca tccagtttac 120

aaggtggggt cccatcaagg ttcagtggca gtggatctgg gacagatttc actctcacca 180

tcagcagtct gcaacctgaa gattttgcaa cttactactg tcaacagagt tacaatgccc 240

cactcacttt cggcggaggg accaaggtgg agatcaaac 279

<210> 18
<211> 92
<212> PRT

<213> Homo sapiens

<400> 18

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr
1 5 10 15

Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
20 25 30

Ile His Val Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
35 40 45

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
50 55 60

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asn Ala Pro
65 70 75 80

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
85 90

<210> 19
<211> 341
<212> DNA
<213> Homo sapiens

<400> 19
cccaggactg gtgaagcctt cggagaccct gtccctcacc tgcactgtct ctggtggctc 60

catcagtagt tactactgga gttggatccg gcagcccccа gggaagggac tggagtggat 120

tgggtatatc tattacagtg ggagcaccaa ctacaacccc tccctcaaga gtcgagtcac 180

catatcagta gacacgtcca agaaccagtt ctccctgaag ctgagttctg tgaccgctgc 240

ggacacggcc gtgtattact gtgccaggac gtatagcagt tcgttctact actacggtat 300

ggacgtctgg ggccaaggga ccacggtcac cgtctcctca g 341

<210> 20
<211> 113
<212> PRT
<213> Homo sapiens

<400> 20

Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val
1 5 10 15

Ser Gly Gly Ser Ile Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro
20 25 30

Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser

35 40 45

Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp
50 55 60

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala
65 70 75 80

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Thr Tyr Ser Ser Ser Phe Tyr
85 90 95

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 21
<211> 274
<212> PRT
<213> Homo sapiens

<400> 21

Ala Gly Ala Gly Cys Cys Ala Cys Cys Cys Thr Cys Thr Cys Cys Thr
1 5 10 15

Gly Thr Ala Gly Gly Gly Cys Cys Ala Gly Thr Cys Ala Gly Ala Gly
20 25 30

Thr Gly Thr Thr Cys Gly Cys Gly Gly Cys Ala Gly Gly Thr Ala Cys
35 40 45

Thr Thr Ala Gly Cys Cys Thr Gly Gly Thr Ala Cys Cys Ala Gly Cys
50 55 60

Ala Gly Ala Ala Ala Cys Cys Thr Gly Gly Cys Cys Ala Gly Gly Cys
65 70 75 80

Thr Cys Cys Cys Ala Gly Gly Cys Thr Cys Cys Thr Cys Ala Thr Cys
85 90 95

Thr Ala Thr Gly Gly Thr Gly Cys Ala Thr Cys Cys Ala Gly Cys Ala
100 105 110

Gly Gly Gly Cys Cys Ala Cys Thr Gly Gly Cys Ala Thr Cys Cys Cys
115 120 125

Ala Gly Ala Cys Ala Gly Gly Thr Thr Cys Ala Gly Thr Gly Gly Cys

130 135 140

Ala Gly Thr Gly Gly Gly Thr Cys Thr Gly Gly Gly Ala Cys Ala Gly
145 150 155 160

Ala Cys Thr Thr Cys Ala Cys Thr Cys Thr Cys Ala Cys Cys Ala Thr
165 170 175

Cys Ala Gly Cys Ala Gly Ala Cys Thr Gly Gly Ala Gly Cys Cys Thr
180 185 190

Gly Ala Ala Gly Ala Thr Thr Thr Thr Gly Cys Ala Gly Thr Gly Thr
195 200 205

Thr Thr Thr Ala Cys Thr Gly Thr Cys Ala Gly Cys Ala Gly Thr Ala
210 215 220

Thr Gly Gly Thr Ala Gly Thr Thr Cys Ala Cys Cys Thr Cys Gly Asn
225 230 235 240

Ala Cys Gly Thr Thr Cys Gly Gly Cys Cys Ala Ala Gly Gly Gly Ala
245 250 255

Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Ala Ala Thr Cys Ala Ala
260 265 270

Ala Cys

<210> 22
<211> 91
<212> PRT
<213> Homo sapiens

<400> 22

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Gly Arg Tyr
1 5 10 15

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
20 25 30

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
35 40 45

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
50 55 60

Glu Asp Phe Ala Val Phe Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Arg

65 70 75 80

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
85 90

<210> 23
<211> 367
<212> DNA
<213> Homo sapiens

<400> 23
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaggt attactggga gtggtggtag tacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatcca 300

gggactacgg tgattatgag ttggttcgac ccctggggcc agggaaccct ggtcaccgtc 360

tcctcag 367

<210> 24
<211> 122
<212> PRT
<213> Homo sapiens

<400> 24

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Thr Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Pro Gly Thr Thr Val Ile Met Ser Trp Phe Asp Pro Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 25
<211> 320
<212> DNA
<213> Homo sapiens

<400> 25
gaactgtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag ttgaaatctg 60

gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc aaagtacagt 120

ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca gagcaggaca 180

gcaaggacag cacctacagc ctcagcagca ccctgacgct gagcaaagca gactacgaga 240

aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc gtcacaaaga 300

gcttcaacag gggagagtgt 320

<210> 26
<211> 106
<212> PRT
<213> Homo sapiens

<400> 26

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 27
<211> 978
<212> DNA
<213> Homo sapiens

<400> 27
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 60

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 120

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 300

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 360

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 420

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 480

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 540

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 600

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 660

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 720

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 780

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 840

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 900

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 960

tccctgtctc cgggtaaa 978

<210> 28
<211> 326
<212> PRT
<213> Homo sapiens

<400> 28

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145 150 155 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
165 170 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
195 200 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys
325

PC32226A.ST25

<210> 29
<211> 296
<212> DNA
<213> Homo sapiens

<400> 29
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120

ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtac catatactac 180

gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagaga 296

<210> 30
<211> 98
<212> PRT
<213> Homo sapiens

<400> 30

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg

<210> 31
<211> 296
<212> PRT
<213> Homo sapiens

<400> 31

Gly Ala Gly Gly Thr Gly Cys Ala Gly Cys Thr Gly Thr Thr Gly Gly
1 5 10 15

Ala Gly Thr Cys Thr Gly Gly Gly Gly Gly Ala Gly Gly Cys Thr Thr
20 25 30

Gly Gly Thr Ala Cys Ala Gly Cys Cys Thr Gly Gly Gly Gly Gly Gly
35 40 45

Thr Cys Cys Cys Thr Gly Ala Gly Ala Cys Thr Cys Thr Cys Cys Thr
50 55 60

Gly Thr Gly Cys Ala Gly Cys Cys Thr Cys Thr Gly Gly Ala Thr Thr
65 70 75 80

Cys Ala Cys Cys Thr Thr Thr Ala Gly Cys Ala Gly Cys Thr Ala Thr
85 90 95

Gly Cys Cys Ala Thr Gly Ala Gly Cys Thr Gly Gly Gly Thr Cys Cys
100 105 110

Gly Cys Cys Ala Gly Gly Cys Thr Cys Cys Ala Gly Gly Gly Ala Ala
115 120 125

Gly Gly Gly Gly Cys Thr Gly Gly Ala Gly Thr Gly Gly Gly Thr Cys
130 135 140

Thr Cys Ala Gly Cys Thr Ala Thr Thr Ala Gly Thr Gly Gly Thr Ala
145 150 155 160

Gly Thr Gly Gly Thr Gly Gly Thr Ala Gly Cys Ala Cys Ala Thr Ala
165 170 175

Cys Thr Ala Cys Gly Cys Ala Gly Ala Cys Thr Cys Cys Gly Thr Gly
180 185 190

Ala Ala Gly Gly Gly Cys Cys Gly Gly Thr Thr Cys Ala Cys Cys Ala
195 200 205

Thr Cys Thr Cys Cys Ala Gly Ala Gly Ala Cys Ala Ala Thr Thr Cys
210 215 220

Cys Ala Ala Gly Ala Ala Cys Ala Cys Gly Cys Thr Gly Thr Ala Thr
225 230 235 240

Cys Thr Gly Cys Ala Ala Ala Thr Gly Ala Ala Cys Ala Gly Cys Cys
245 250 255

Thr Gly Ala Gly Ala Gly Cys Cys Gly Ala Gly Gly Ala Cys Ala Cys
260 265 270

Gly Gly Cys Cys Gly Thr Ala Thr Ala Thr Thr Ala Cys Thr Gly Thr
275 280 285

Gly Cys Gly Ala Ala Ala Gly Ala
290 295

<210> 32
<211> 98
<212> PRT
<213> Homo sapiens

<400> 32

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys

<210> 33
<211> 296
<212> DNA
<213> Homo sapiens

<400> 33
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagaga 296

<210> 34

<211> 98
<212> PRT
<213> Homo sapiens

<400> 34

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg

<210> 35
<211> 293
<212> DNA
<213> Homo sapiens

<400> 35
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 36
<211> 97
<212> PRT
<213> Homo sapiens

<400> 36

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr

20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg

<210> 37
<211> 290
<212> PRT
<213> Homo sapiens

<400> 37

Gly Ala Ala Ala Thr Thr Gly Thr Gly Thr Thr Gly Ala Cys Gly Cys
1 5 10 15

Ala Gly Thr Cys Thr Cys Cys Ala Gly Gly Cys Ala Cys Cys Cys Thr
20 25 30

Gly Thr Cys Thr Thr Thr Gly Thr Cys Thr Cys Cys Ala Gly Gly Gly
35 40 45

Gly Ala Ala Ala Gly Ala Gly Cys Cys Ala Cys Cys Cys Thr Cys Thr
50 55 60

Cys Cys Thr Gly Cys Ala Gly Gly Gly Cys Cys Ala Gly Thr Cys Ala
65 70 75 80

Gly Ala Gly Thr Gly Thr Thr Ala Gly Cys Ala Gly Cys Ala Gly Cys
85 90 95

Thr Ala Cys Thr Thr Ala Gly Cys Cys Thr Gly Gly Thr Ala Cys Cys
100 105 110

Ala Gly Cys Ala Gly Ala Ala Ala Cys Cys Thr Gly Gly Cys Cys Ala
115 120 125

Gly Gly Cys Thr Cys Cys Cys Ala Gly Gly Cys Thr Cys Cys Thr Cys

130 135 140

Ala Thr Cys Thr Ala Thr Gly Gly Thr Gly Cys Ala Thr Cys Cys Ala
145 150 155 160

Gly Cys Ala Gly Gly Gly Cys Cys Ala Cys Thr Gly Gly Cys Ala Thr
165 170 175

Cys Cys Cys Ala Gly Ala Cys Ala Gly Gly Thr Thr Cys Ala Gly Thr
180 185 190

Gly Gly Cys Ala Gly Thr Gly Gly Gly Thr Cys Thr Gly Gly Gly Ala
195 200 205

Cys Ala Gly Ala Cys Thr Thr Cys Ala Cys Thr Cys Thr Cys Ala Cys
210 215 220

Cys Ala Thr Cys Ala Gly Cys Ala Gly Ala Cys Thr Gly Gly Ala Gly
225 230 235 240

Cys Cys Thr Gly Ala Ala Gly Ala Thr Thr Thr Thr Gly Cys Ala Gly
245 250 255

Thr Gly Thr Ala Thr Thr Ala Cys Thr Gly Thr Cys Ala Gly Cys Ala
260 265 270

Gly Thr Ala Thr Gly Gly Thr Ala Gly Cys Thr Cys Ala Cys Cys Thr
275 280 285

Cys Cys
290

<210> 38
<211> 96
<212> PRT
<213> Homo sapiens

<400> 38

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser

50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

<210> 39
<211> 288
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (288)..(288)
<223> n is a, c, g, or t

<400> 39
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataatagtt accctccn 288

<210> 40
<211> 96
<212> PRT
<213> Homo sapiens

<400> 40

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Pro
85 90 95

<210> 41
<211> 288
<212> DNA
<213> Homo sapiens

<400> 41
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctcch 288

<210> 42
<211> 96
<212> PRT
<213> Homo sapiens

<400> 42

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

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<213> Homo sapiens

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gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

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<211> 97
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<400> 44

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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
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Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

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<211> 470
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<213> Homo sapiens

<400> 45

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Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala

65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys Asp Leu Gly Trp Ser Asp Ser Tyr Tyr Tyr Tyr
115 120 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
130 135 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145 150 155 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
165 170 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
180 185 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
195 200 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
210 215 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225 230 235 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
275 280 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
325 330 335

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340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
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<210> 46
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<212> PRT
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<400> 46

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Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys Gly Tyr Ser Ser Gly Trp Tyr Tyr Tyr Tyr Tyr
115 120 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
130 135 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145 150 155 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
165 170 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
180 185 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
195 200 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
210 215 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225 230 235 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
275 280 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

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450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 47
<211> 236
<212> PRT
<213> Homo sapiens

<400> 47

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu His Arg Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

His Asn Ser Tyr Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 48
<211> 236
<212> PRT
<213> Homo sapiens

<400> 48

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

His Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 49
<211> 470
<212> PRT
<213> Homo sapiens

<400> 49

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

Val Gln Cys Gln Ala Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

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Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Val Arg Asp Gly Val Glu Thr Thr Phe Tyr Tyr Tyr Tyr
        115                 120                 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
    130                 135                 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145                 150                 155                 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        195                 200                 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
    210                 215                 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225                 230                 235                 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        275                 280                 285
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Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 50
<211> 473
<212> PRT
<213> Homo sapiens

<400> 50

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Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Val Leu Arg Phe Leu Glu Trp Leu Leu Tyr Tyr
115 120 125

Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145 150 155 160

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
195 200 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
210 215 220

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
225 230 235 240

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
245 250 255

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 51
<211> 236
<212> PRT
<213> Homo sapiens

<400> 51

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20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Phe Thr Cys Arg Ala Ser
35 40 45

Gln Asp Ile Arg Arg Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

His Asn Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val Glu Ile
115 120 125

Ile Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 52
<211> 236
<212> PRT
<213> Homo sapiens

<400> 52

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

1 5 10 15

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20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

His Asn Ser Tyr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 53
<211> 326
<212> DNA
<213> Artificial Sequence

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<220>
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<223> n is a, c, g, or t

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gggaaagcyc ctaagcgcct gatctatgct gcatccmrwt trcammgwgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcmg cctgcagcct 240

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<211> 322
<212> DNA
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gggaaagccc ctaarctcct gatcyatgyt gcatccagtt trcaargtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

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gggaccaagg tggagatcaa ac 322

<210> 55
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
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<221> misc_feature
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cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

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caagggacca aggtggaaat caaac 325

<210> 56
<211> 376
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Consensus Sequence

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tcctgtgcag cctctggatt cacyttcagt gactactaya tgagctggat ccgccaggct 120

ccagggaagg ggctggartg ggtttcatac attagtagta gtggtagtac cakakactac 180

gcagactctg tgaagggccc attcaccatc tccagggaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgy gagagatgga 300

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gtcaccgtct cctcag 376

<210> 57
<211> 358
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Consensus Sequence

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<221> misc_feature
<222> (337)..(337)
<223> n is a, c, g, or t

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acctgcactg tctctggtgg ctccatcagt arttactact ggagctggat ccggcagccc 120

gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcmc caactacaac 180

ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgarct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcggt aacgattttt 300

ggagtggtta ttatctttga ctactggggc cagrganccc tggtcaccgt ctcctcag 358

PC32226A.ST25

<210> 58
<211> 418
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Consensus Sequence

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tcctgtrcag cctctggatt cacctttagc agctatgcca tgarctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagst attastggka gtggtggtab yacatwctac 180

gcagactccg tgaagggccc gttcaccatc tccagagaca attccargam cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatctk 300

ggctrsksyg actyttacta ctactactac ggtatggacg tctggggcca agggacyacg 360

gtgattatga gttggttcga cccctggggc cagggaaccc tggtcaccgt ctcctcag 418

<210> 59
<211> 364
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Consensus Sequence

<400> 59
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ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgact caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagyt ctgtgaccgc tgcggacacg gccgtgtatt actgtgccag gacgtatagc 300

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tcag 364

<210> 60
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Consensus Sequence

<400> 60

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

INTERNATIONAL SEARCH REPORT

Int nal Application No
P..../EB2005/002096

A. CLASSIFICATION OF SUBJECT MATTER
A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BENINI S ET AL: "INHIBITION OF INSULIN-LIKE GROWTH FACTOR I RECEPTOR INCREASES THE ANTITUMOR ACTIVITY OF DOXORUBICIN AND VINCRISTINE AGAINST EWING'S SARCOMA CELLS" CLINICAL CANCER RESEARCH, THE ASSOCIATION, DENVILLE, NJ, US, vol. 7, no. 6, June 2001 (2001-06), pages 1790-1797, XP001187566 ISSN: 1078-0432 Tables 1 and 2 and discussion ----- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2005	22/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Renggli, J

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LU D ET AL: "Simultaneous blockade of both the epidermal growth factor receptor and the insulin-like growth factor receptor signaling pathways in cancer cells with a fully human recombinant bispecific antibody" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 279, no. 4, 23 January 2004 (2004-01-23), pages 2856-2865, XP002316541 ISSN: 0021-9258 page 2861-seq, "Inhibition of tumor cell proliferation in vitro by the BsAb"; page 2857, right-hand column, experimental procedures, Cell lines and proteins; discussion	1-16
X	US 2004/086503 A1 (COHEN BRUCE D ET AL) 6 May 2004 (2004-05-06) '0032!,'0127!, '0198!, '0216!, '0218!, '0237!, '0239!, examples IX, XI, XII, XIII, XIV, XVIII	1-16
X	YE J-J ET AL: "COMBINED EFFECTS OF TAMOXIFEN AND A CHIMERIC HUMANIZED SINGLE CHAIN ANTIBODY AGAINST THE TYPE I IGF RECEPTOR ON BREAST TUMOR GROWTH IN VIVO" HORMONE AND METABOLIC RESEARCH, THIEME-STRATTON, STUTTGART, DE, vol. 35, no. 11/12, November 2003 (2003-11), pages 836-842, XP009055889 ISSN: 0018-5043 abstract	1-16
X	MALONEY E K ET AL: "An anti-insulin-like growth factor I receptor antibody that is a potent inhibitor of cancer cell proliferation" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 63, no. 16, 15 August 2003 (2003-08-15), pages 5073-5083, XP002978956 ISSN: 0008-5472 page 5075, right-hand column, 6th paragraph and page 5079-5080, "In vivo effect of EM164 on BxPC-3.....; abstract	1-16
X	US 2003/165502 A1 (FUJITA-YAMAGUCHI YOKO) 4 September 2003 (2003-09-04) '0006!, '0015!-'0016!, examples 7 and 8	1-16

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/235582 A1 (SINGH RAJEEVA ET AL) 25 December 2003 (2003-12-25) '0124-0129!	1-16
P,X	WO 2005/016967 A (PFIZER PRODUCTS INC; COHEN, BRUCE, DAVID; BEDIAN, VAHE) 24 February 2005 (2005-02-24) the whole document	1-16
P,X	WO 2005/016970 A (IMCLONE SYSTEMS INCORPORATED; LUDWIG, DALE, L) 24 February 2005 (2005-02-24) the whole document	1-16

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/IB2005/002096

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

nation on patent family members

Inte[illegible]nal Application No
PC[illegible]B2005/002096

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